

**Impact of mesial temporal lobe damage on memory and social-cognitive processing:
Neurobehavioral and psychophysiological findings from patients with chronic mesial
temporal lobe epilepsy and Urbach-Wiethe disease**

Thesis (cumulative thesis)

Presented to the Faculty of Arts and Social Sciences
of the University of Zurich
for the Degree of Doctor of Philosophy

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Accepted in the Spring Term 2015
on the Recommendation of the Doctoral Committee:

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Zurich, 2015

Acknowledgments

I would like to express my deep gratitude to everyone who supported me throughout my PhD.

First of all, I would like to thank Prof. Hennric Jokeit from the Swiss Epilepsy Center in Zurich for having been such a competent, supportive, and interested supervisor. During the entire period of my PhD I have benefited from his broad and impressive clinical and scientific expertise. Thank you, Hennric, for helping me initiate our study on Urbach-Wiethe disease in South Africa and for supporting me throughout the project. I am very pleased to have had the opportunity to realize such an exciting and unique study during my PhD. Thank you for having always been available for questions and inspiring discussions, for the great amount of time you invested in my supervision, for your continuing encouragement during the tough process of publishing, for your trust, and for your understanding in many ways and situations.

I sincerely thank Prof. Martin Meyer from the Department of Psychology at the University of Zurich for his external supervision of my PhD, for providing such a comfortable atmosphere during my presentations at his weekly seminars, and for being a very benevolent and respectful professor.

I also sincerely thank Prof. Peter Brugger from the University Hospital Zurich for having been a member of my ZNZ committee and for having read and approved my progress reports and final thesis.

I cordially thank Prof. Katherine P. Rankin and Dr. Babu Adhimoolam from the Memory and Aging Center at the University of California San Francisco. Thank you, Kate, for your interest in our research, for many valuable contributions and advice on our studies, and for having been one of the committee members of my Neuroscience PhD Program. Your knowledge and your expertise are impressive and I feel very honored to have been able to work with such a successful researcher throughout my PhD. Thank you, Adhi, for teaching me so much about functional imaging and voxel-based morphometry, for answering my numerous questions and for providing many interesting discussions via skype. You have been a very reliable, patient, and kind colleague from overseas.

Warmest thanks to Dr. Victoria Ives-Deliperi and Dr. James Butler from Mediclinic Constantiaberg in Cape Town who greatly helped us establish the Urbach-Wiethe project. Thank you for initiating the collaboration with local researchers and for your careful study organization on site. Thank you, Vicki, for your impressive Afrikaans translations and for recruiting the control subjects within a very short period of time. Thank you, Vicki and James, for having provided such an interesting and welcoming South African research environment and for sharing your passion for the human brain with me.

Many cordial thanks to Dr. Laurie Rauch and Robert Evans from the Sports Science Institute at the University of Cape Town for providing the ECG equipment, and for your help with data acquisition and analyses. I was very impressed by your interest in our study and by your kindness to help us with anything we needed. Our successful international collaboration was a very positive experience for me and made my research stays in Cape Town even more memorable.

I express my warmest thanks to Thekla Kaisen, Jasmina Dracic-Sacirovic, Theresa Biesold, and Dr. Dominik Huber from the MRI Institute at Schulthess Clinic in Zurich for having provided a very professional and helpful MRI environment. Thank you, Thekla, Jasmina, and Theresa for spending numerous evenings and Saturdays scanning patients and controls with me. Thank you all for your thorough, reliable, and excellent work, and for sharing many enjoyable moments.

Thanks to the best team, the “NPSY-Team” from the Swiss Epilepsy Center, for such a familiar and pleasant working atmosphere, for many happy lunch and coffee breaks, and for the support in both career and private terms.

Thanks to the Swiss Epilepsy Foundation for the generous funding of my PhD, including attendance fees and travel expenses for many national and international conferences.

Last but not least, many thanks to my dear parents, to Isabella and Adrian, and to all my great friends who supported me during all stages of my PhD.

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Summary

Mesial temporal lobe epilepsy (MTLE) and Urbach-Wiethe disease (UWD) are two disorders that are associated with focal and progressive damage to mesial temporal lobe structures. Consequently, the cognitive profiles of affected patients are frequently characterized by deficits in long-term memory and social cognition. Although both disorders have made important contributions to our knowledge of mesial temporal lobe functions, their impact particularly on social-cognitive processing is still underinvestigated. Using behavioral, neuroimaging, and psychophysiological measures, the main objective of the present thesis was to investigate the impact of MTLE and UWD on memory and social-cognitive processing. This thesis provides new clinical findings that may help clinicians in terms of diagnosis and therapy of rare patients with chronic MTLE and accompanying congenital blindness. Moreover, the current data confirm and extend previous research on social cognition in MTLE by showing that RMTLE is a specific risk factor for reduced empathy towards the internal states of others. The converging neurobehavioral and psychophysiological findings from the two complementary lesion models emphasize that amygdala-brainstem dysfunctions constitute a major cause of impaired social cognition in MTLE and UWD. Overall, the present thesis contributes to our theoretical and clinical understanding of cognitive comorbidities in MTLE and UWD, and provides new lesion data on specific functions of the mesial temporal lobes and related connections.

Zusammenfassung

Die mesiale Temporallappenepilepsie (MTLE) und die Urbach-Wiethe-Erkrankung (UWE) sind zwei Krankheiten, die mit einer fokalen und fortschreitenden Schädigung im mesialen Temporallappen einhergehen. Die dabei betroffenen Hirnregionen sind für die Bildung des Langzeitgedächtnisses und für sozial-kognitive Prozesse von zentraler Bedeutung. Obwohl beide Erkrankungen massgeblich zum Verständnis der Funktionen des mesialen Temporallappens beigetragen haben, sind deren Auswirkungen insbesondere auf die soziale Kognition noch wenig bekannt. Die vorliegende Arbeit hatte zum Ziel, die Einflüsse der MTLE und der UWE auf bestimmte Prozesse des Gedächtnisses und der sozialen Kognition zu untersuchen. Dazu wurden Verhaltensmasse sowie bildgebende und psychophysiologische Verfahren eingesetzt. Die dabei gewonnen Erkenntnisse könnten dazu beitragen, die Diagnostik und Therapie von seltenen Patienten mit einer MTLE und einer gleichzeitig vorhandenen kongenitalen Blindheit zu verbessern. Zudem zeigen die Befunde, dass die rechtsseitige MTLE mit einem erhöhten Risiko für eine verminderte Empathiefähigkeit verbunden ist. Die konsistenten neurobehavioralen und psychophysiologischen Daten der beiden komplementären Läsionsmodelle verdeutlichen, dass der Amygdala und deren Projektionen zum Hirnstamm eine entscheidende Rolle bei der Entstehung sozial-kognitiver Defizite im Rahmen der MTLE sowie der UWE zukommen. Die vorliegende Arbeit leistet einen Beitrag zum theoretischen und klinischen Verständnis kognitiver Beeinträchtigungen von Patienten mit einer MTLE und einer UWE und zeigt neue Erkenntnisse hinsichtlich bestimmter Funktionen des mesialen Temporallappens und dessen Projektionen auf.

Abbreviations

AEDs: antiepileptic drugs

AI: anterior insula

BLA: basolateral amygdala

BOLD: blood oxygenation level dependent

CM: centromedial amygdala

ECG: electrocardiogram

fMRI: functional magnetic resonance imaging

HRV: heart rate variability

HS: hippocampal sclerosis

LMTLE: left mesial temporal lobe epilepsy

MTLE: mesial temporal lobe epilepsy

PAG: midbrain periaqueductal gray

RMTLE: right mesial temporal lobe epilepsy

ToM: theory of mind

UWD: Urbach-Wiethe disease

VBM: voxel-based morphometry

1 General introduction and thesis outline

Refractory¹ mesial temporal lobe epilepsy (MTLE) and Urbach-Wiethe disease (UWD) are two chronic disorders that are associated with focal and progressive damage to mesial temporal lobe structures. The mesial temporal lobe is a complex brain system that plays a key role for the formation of long-term memories and for the processing of social and emotional² information. Consequently, the cognitive profiles of patients with MTLE and UWD are frequently characterized by deficits in long-term memory and social cognition, which highly interferes with the professional and social lives of affected patients. In order to develop appropriate diagnostic tools and treatment approaches for patients with MTLE and UWD, more insight is needed into the nature and etiopathogenesis of cognitive³ impairments often accompanying MTLE and UWD.

Using behavioral, neuroimaging, and psychophysiological measures, the main objective of the present thesis was to investigate the impact of MTLE and UWD on memory and social-cognitive processing. Therefore, this work intended to shed new light on the complex nature and etiopathogenesis of cognitive impairments frequently associated with MTLE and UWD. Further, the present work aimed to provide comparative and complementary data on the impact of focal unilateral and focal bilateral mesial temporal lobe damage on memory and social-cognitive processing. In this way, the current thesis contributes to our clinical understanding of cognitive comorbidities in patients with MTLE and UWD, and provides new insights into certain functions of the mesial temporal lobes and related connections.

1.1 Mesial temporal lobe

The mesial temporal lobe is a brain system of anatomically related regions including the hippocampus, the parahippocampal gyrus, and the amygdala. Brenda Milner's famous studies in a unique case, known as patient HM, have provided seminal insights into the functions of the mesial temporal lobe and the organization of human memory (Scoville & Milner, 1957; Milner,

¹ In this thesis, the terms medically refractory and chronic are used interchangeably.

² In this thesis, the terms emotion/emotional and affect/affective are used interchangeably.

³ In this thesis, the terms cognitive and cognition refer to both "classic" (e.g., memory, language, executive functions) and social-cognitive functions.

1972). Following bilateral mesial temporal lobe resection for the relief of drug-resistant epilepsy, patient HM suffered from global anterograde amnesia. Surprisingly, HM's intellectual functions and implicit memory including skill learning, simple classical conditioning, and perceptual priming were relatively unaffected (Corkin, 1984). This selective and irreversible loss of anterograde episodic memory after bilateral mesial temporal lobe resection provided the first human lesion evidence for the key role of the mesial temporal lobe for episodic memory and demonstrated the existence of different memory systems in the human brain.

Numerous subsequent experimental animal studies and neuropsychological studies in amnesic patients with either unilateral or bilateral mesial temporal lobe damage have supported and extended the pioneering insights gained from patient HM (e.g., Penfield & Milner, 1958; Hyman, Van Hoesen, Damasio, & Barnes, 1984; Squire, Zola-Morgan, & Chen, 1988; Squire, 1992; Zola-Morgan, Squire, & Ramus, 1994; Winocur, McDonald, & Moscovitch, 2001). These studies have confirmed Milner's seminal finding that lesions in the bilateral mesial temporal lobe cause a complete loss of anterograde episodic memory and have further shown that unilateral damage, however, involves only material-specific memory deficits. Thus, left-lateralized lesions have been found to affect predominantly long-term memory for verbal information, and right-lateralized lesions to affect mainly long-term memory for visual-spatial information. Moreover, episodic memory impairments following mesial temporal lobe damage have been shown to be independent from the sensory modality in which information is presented (Milner, 1972; Squire, Schmolck, & Stark, 2001), which is attributable to the convergence of polymodal sensory input into the different regions of the mesial temporal lobes (Lavenex & Amaral, 2000).

Research in both animals and humans with varying extent of mesial temporal lesions have further shown that each structure of the mesial temporal lobe is differentially involved in the formation of episodic memories. It is now well established that the hippocampus and the parahippocampal gyrus represent core memory regions that are essential for encoding and consolidation of new episodic information (Squire, 1992; Schacter & Tulving, 1994). This process of episodic memory formation is influenced by the amygdala, one of the core affective regions of our brain (Pessoa, 2008; Adolphs, 2009; Pessoa, 2010), which functions to enhance memory encoding and consolidation by moderating the valence and arousal of emotional information

(Cahill, Prins, Weber, & McGaugh, 1994; Adolphs, Cahill, Schul, & Babinsky, 1997; van Stegeren, Everaerd, & Gooren, 2002; Dolcos, LaBar, & Cabeza, 2004; Hurlemann et al., 2007).

Besides its involvement in emotional memory, the amygdala plays a major role for emotional and social behavior (LeDoux, 1996; Lieberman, 2007; Adolphs, 2010). Despite that patient HM's temporal lobe resection included the bilateral amygdala, his personality was described as even-tempered and well-behaved (Corkin, 1984). However, due to the absence of social-cognitive neuroscience at that time, there was no theoretical and methodological framework to systematically investigate HM's social-cognitive functions. The classic studies of Klüver and Bucy (1937, 1939) were the first to describe profound behavioral changes after large bilateral mesial temporal lobe lesions in monkeys, including excessive oral behaviors as well as changes in fear reactivity and sexual behavior. Subsequently, converging evidence from neuroimaging and lesion studies in humans have clearly demonstrated that the amygdala is intimately linked to various fear-related processes, including fear conditioning, fear recognition, and fear experience (e.g., Adolphs, Tranel, Damasio, & Damasio, 1994; Bechara et al., 1995; Breiter et al., 1996; Morris et al., 1996; Whalen et al., 1998; Tranel, Gullikson, Koch, & Adolphs, 2006). This historical conceptualization of the amygdala as a fear module has more recently been extended to a more general role in salience processing and to a bridging function between emotion, cognition, and behavior (Adolphs, 2001; Seeley et al., 2007; Pessoa, 2008; Pessoa, 2010). In this way, the amygdala crucially contributes to and shapes our emotional and social behavior, attention, perception, and memory.

This proposed integrative role of the amygdala is clearly reflected in the region's anatomy. Based on functional network analyses (Guimera & Amaral, 2005), the amygdala is considered one of the most highly interconnected regions of our brain, showing extensive cortical and subcortical projections (Young, Scanneil, Burns, & Blakemore, 1994). Moreover, its connectivity topology is suggested to resemble a connector hub (Sporns, Honey, & Kötter, 2007) that links and effectively integrates information from distinct provincial hub regions (Pessoa, 2008; Pessoa, 2010; Bickart, Hollenbeck, Barrett, & Dickerson, 2012). The amygdala is a complex structure containing more than a dozen nuclei that are highly interconnected and that have their own connection patterns. In terms of both anatomy and function, the amygdala consists of two main subdivisions: one involving the basolateral amygdala (BLA) and one involving the

centromedial amygdala (CM; LeDoux, 1996; Aggleton & Saunders, 2000; Davis & Whalen, 2001). The BLA receives vast polymodal sensory input from the cortex allowing the region to process a stimulus according to its salience and relevance. By contrast, the CM is sometimes regarded as the “controller of the brainstem” (Cardinal, Parkinson, Hall, & Everitt, 2002) that uses its projections to different regions of the brainstem to coordinate behavioral, autonomic, and neuroendocrine responses to any kind of salient stimulus (Figure 1).

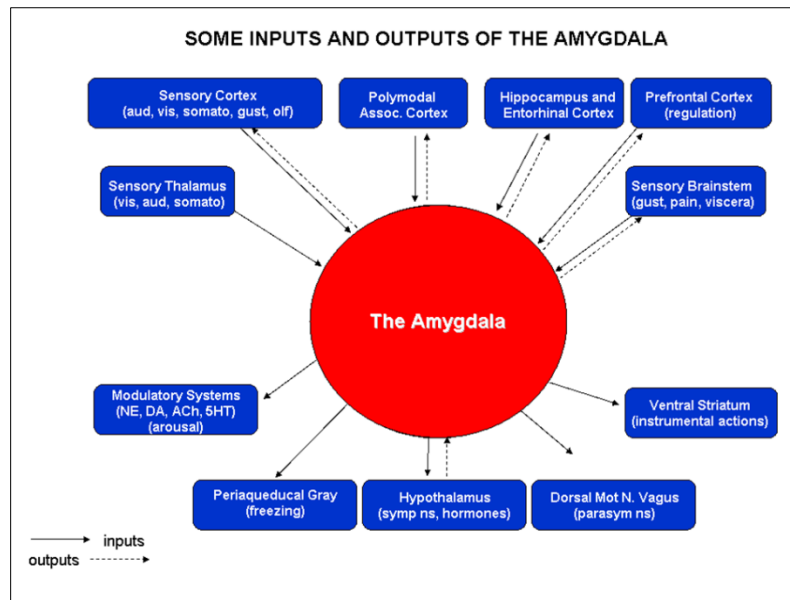


Figure 1. Major input and output connections of the amygdala. *Abbreviations:* aud, auditory; vis, visual; somato, somatosensory; gust, gustatory; olf, olfactory; NE, norepinephrine; DA, dopamine; ACh, acetylcholine; 5HT, serotonin (LeDoux, 2008).

While structural and functional neuroimaging studies of healthy controls provide important correlational information on the neuronal underpinnings of cognitive processes, only human lesion studies provide the final evidence on the causal relationships between particular brain regions and particular cognitive functions. Initiated by the pioneering findings from patient HM, much of our current understanding on episodic memory has been derived from neuroimaging and neuropsychological studies in patients with circumscribed mesial temporal lobe damage due to chronic MTLE. Another disorder that has provided important insights into the functions of the mesial temporal lobe, particularly in terms of emotional memory and social cognition, is the unique disorder of UWD that is associated with selective bilateral amygdala damage.

Although both disorders have crucially contributed to the current knowledge of mesial temporal lobe functions, their impact particularly on social-cognitive processing is still underinvestigated.

1.2 Mesial temporal lobe epilepsy

Epilepsy is a common neurological disorder that has a prevalence of about 0.5-1.0% (Sander, 2003). The term epilepsy refers to the presence of unprovoked and repetitive epileptic seizures that are symptoms of transient or chronic brain pathology of various origins (International League Against Epilepsy, ILAE). Epilepsies are either genetically determined (idiopathic) or possibly caused by an underlying brain lesion (cryptogenic) or certainly caused by an underlying brain lesion (symptomatic; Bancaud et al., 1981). While idiopathic epilepsies are typically associated with seizures that affect the whole brain (generalized epilepsies), symptomatic epilepsies are usually associated with seizures that originate from a circumscribed brain region (focal epilepsies). MTLE is the most prevalent focal epilepsy in adults, which frequently starts within the first decade of life and is often characterized by hippocampal sclerosis (HS; Engel, 1996). Because of its high prevalence (50-75% of treated cases in epilepsy surgery centers had temporal lobe epilepsy; Téllez-Zenteno & Hernández-Ronquillo, 2011) and its high potential for drug-resistance, MTLE is of clinical significance.

Although the most obvious symptom of untreated or chronic epilepsy is the presence of recurrent seizures, different types of epilepsies are often accompanied by neurobehavioral comorbidities, including psychiatric disorders, adverse psychosocial consequences, and cognitive impairments (Elger, Helmstaedter, & Kurthen, 2004; Hermann, Seidenberg, & Jones, 2008; Kanner, 2009). Depression and anxiety are the most common psychiatric comorbidities in patients with epilepsy and their prevalence is increased compared to the general population and to patients with other chronic neurological disorders (Hermann et al., 2008; Kanner, 2009; Kanner et al., 2012). The high comorbidity of epilepsy and depression is suggested to be primarily related to common neuropathological mechanisms rather than to be a complication of the underlying seizure disorder (Kanner et al., 2012). Because brain pathology in MTLE affects mesial-temporal lobe regions that are part of the limbic system, symptoms of depression and anxiety are particularly frequent in patients with MTLE (Perini et al., 1996; Quiske, Helmstaedter, Lux, & Elger, 2000). As comorbid depression in epilepsy is not only associated

with poor quality of life but also with poor response to medical and surgical treatment (Kanner, 2009; Kanner et al., 2012), it is important that comorbid depressive symptoms are recognized and adequately treated.

A series of survey-based studies have investigated the prevalence of psychosocial consequences that are frequently associated with epilepsy (Kobau et al., 2004; Strine et al., 2005; Kobau, Gilliam, & Thurman, 2006; Kobau et al., 2007). Accordingly, people with epilepsy reported higher unemployment rates, lower income and education, and were more often single than people without epilepsy. These findings highlight the profound impact of epilepsy on the lives of affected people and also demonstrate that epilepsy is associated with major challenges for society. Whether such maladaptive behavioral outcome is caused mainly by social stigmatization, model learning or the underlying brain pathology is still a matter of ongoing controversy.

The cognitive profiles of epilepsy patients are very heterogeneous and depend on the particular epilepsy type (Elger et al., 2004). The effect of epilepsy on cognition is best understood in MTLE, which is attributable to the focal damage of the mesial temporal lobe that is, as stated above, responsible for the formation of episodic memories. In the following, “classic” cognitive functions such as memory and executive functions are distinguished from social-cognitive functions.

1.2.1 “Classic” cognitive functions

The most common cognitive deficits found in patients with MTLE are episodic memory impairments, which is consistent with the crucial involvement of the hippocampus and other mesial temporal lobe structures for the formation of anterograde episodic memory. Because verbal episodic memory functions are strongly related to the language-dominant hemisphere, left mesial temporal lobe epilepsy (LMTLE) is typically associated with material-specific deficits in verbal episodic memory (Helmstaedter, Grunwald, Lehnertz, Gleißner, & Elger, 1997; Hermann, Seidenberg, Schoenfeld, & Davies, 1997). In the presence of left-hemisphere language dominance, an analogous association between right mesial temporal lobe epilepsy (RMTLE) and visual episodic memory impairments has been demonstrated, although the findings are less consistent than for LMTLE (Alessio et al., 2004; Gleissner, Helmstaedter, Schramm, & Elger,

2004). The frequent absence of non-verbal memory impairment in RMTLE is probably attributable to the use of covert verbalization strategies in non-verbal memory tasks and to the presence of more distributed networks for non-verbal than for verbal memory (Elger et al., 2004).

However, the “classic” cognitive deficits associated with chronic MTLE are not restricted to the domain of episodic memory but also often affect generalized cognitive and executive functions (Jokeit, Ebner, et al., 1997; Jokeit & Ebner, 1999; Oyegbile et al., 2004). The frequent occurrence of such non-memory deficits is at least partly attributable to structural and functional brain changes that extend to regions outside the epileptogenic mesial temporal lobe, particularly to the lateral temporal and frontal lobes (Arnold et al., 1996; Jokeit, Seitz, et al., 1997; Takaya et al., 2006; Focke et al., 2008; Keller & Roberts, 2008). One major reason for such extramesial temporal lobe damage and dysfunction is that propagation of interictal epileptic discharges and temporal lobe seizures, and therefore seizure toxicity (Riederer et al., 2008; Bonilha et al., 2010), follow a posterior-anterior gradient (Lieb, Dasheiff, & Engel, 1991; Emerson, Turner, Pedley, Walczak, & Forgiione, 1995). Due to the tight interconnections between the temporal and frontal lobes, another factor that is likely to contribute to the presence of brain damage and dysfunction in anatomically remote regions is hippocampal deafferentation (Bonilha, Rorden, Castellano, Cendes, & Li, 2005; Bonilha et al., 2010).

However, mesial temporal lobe damage per se and the adverse effect of recurrent seizures and interictal epileptic discharges on the structure and function of remote brain regions are not the only factors that contribute to the occurrence of cognitive deficits in MTLE (Figure 2, p. 16). Although largely reversible, the treatment with antiepileptic drugs (AEDs; Loring, Marino, & Meador, 2007) and the presence of comorbid psychiatric disorders, particularly of depression, are also likely to have an adverse impact on patients’ cognition (Paradiso, Hermann, Blumer, Davies, & Robinson, 2001).

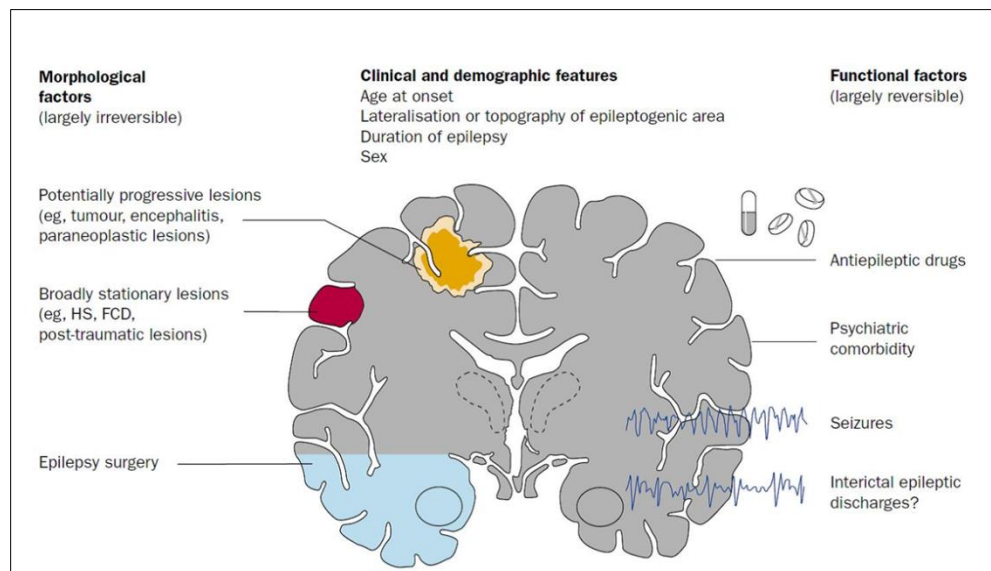


Figure 2. Epilepsy-related morphological, clinical, and functional factors that affect cognitive functions in chronic epilepsy such as MTLE (Elger et al., 2004).

Other influential factors to consider are age at epilepsy onset and duration of epilepsy, with cross-sectional and longitudinal evidence showing that patients with earlier epilepsy onset and longer disease duration have the worst cognitive outcome (Jokeit & Ebner, 1999; Hermann, Seidenberg, & Bell, 2002; Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003). Early-onset epilepsies that persist despite drug and surgical treatments have a particularly negative impact on patients' cognition. The reason is that persisting seizures are associated with progressive brain damage, a process that also affects non-epileptic regions and that is likely to interfere with functional compensatory mechanisms (Hermann et al., 2002; Lespinet, Bresson, N'Kaoua, Rougier, & Claverie, 2002). The few studies that have investigated the influence of sex on verbal episodic memory in MTLE suggest that women benefit to a greater extent from atypical language dominance than men, because language in women is more bilaterally organized than in men (Helmstaedter, 1999; Helmstaedter, Brosch, Kurthen, & Elger, 2004).

Due to the complex etiopathogenesis of cognitive deficits in epilepsy, which involves various interacting morphological, clinical, and functional factors, research on cognition in epilepsy patients need to consider and separate these potentially influencing factors as much as possible.

1.2.2 Risk assessment of postsurgical amnesia

Because MTLE has a high potential for drug-resistance, epilepsy surgery is a successful treatment option for a large proportion of patients with unilateral MTLE. However, one major risk of mesial temporal lobe resections, of both selective amygdalohippocampectomy and anterior temporal lobectomy, is the occurrence of postsurgical deficits in anterograde episodic memory (Selwa et al., 1994; Clusmann et al., 2002; Stroup et al., 2003; Helmstaedter, Van Roost, et al., 2004). Previous research has demonstrated that particularly LMTLE patients with left-hemisphere language dominance and a high presurgical memory performance are at increased risk for postsurgical deficits in verbal episodic memory (Jokeit, Ebner, et al., 1997; Rausch et al., 2003; Gleissner et al., 2004). Because memory loss in patients with MTLE can highly affect their quality of life, professional success, and social relationships (Fraser, 1993), it is essential to assess the individual risk for postsurgical episodic memory impairments during comprehensive presurgical evaluation.

Thus, standard verbal and non-verbal memory tests are used to assess the presurgical memory performance of patients, which helps to identify those patients with relatively preserved memory who are at increased risk for postsurgical memory loss. However, as stated above, the benefit of neuropsychological memory tests to lateralize MTLE is limited, particularly in RMTLE patients with left-hemisphere language dominance. In this regard, functional magnetic resonance imaging (fMRI) is a very useful non-invasive imaging technique to functionally map eloquent brain regions, including language, sensorimotor, visual, and memory areas. In order to estimate a single patient's risk for postsurgical memory impairment using fMRI, a task is required that activates the bilateral mesial temporal lobe in individual healthy subjects. In this regard, the recall of complex visual-spatial memories in particular has been shown to be associated with activity in the bilateral mesial temporal lobe (Maguire et al., 1998; Grady, McIntosh, Rajah, Beig, & Craik, 1999). Based on this knowledge, previous fMRI studies have applied the Roland's Home Town Walking task (Roland, Eriksson, Stone-Elander, & Widen, 1987), a visual-spatial memory task that involves the mental navigation and imagery of landmarks, to healthy subjects and to patients with unilateral MTLE (Jokeit, Okujava, & Woermann, 2001; Janszky et al., 2004; Janszky et al., 2005; Avila et al., 2006; Schacher, Haemmerle, et al., 2006). These studies have consistently shown that in healthy controls the recall of familiar routes is associated with almost

symmetric activity in the bilateral mesial temporal lobe, including the hippocampus and parahippocampal gyrus. By contrast, in the majority of patients with unilateral MTLE, an asymmetric activation of the right and left mesial temporal lobe was identified, with pathologically reduced activity found in the epileptogenic mesial temporal lobe. These findings demonstrate that the Roland's Hometown Walking task is a valid and reliable method to lateralize unilateral MTLE. Importantly, the task has also been shown to predict postsurgical memory outcome in patients with RMTLE (Janszky et al., 2005), which highlights the paradigms' diagnostic value for the presurgical memory lateralization in individual patients with unilateral MTLE.

1.2.3 Social-cognitive functions

While the “classic” cognitive functions such as language, perception, attention, and particularly memory have been well-studied in MTLE, less is known about the impact of the disorder on the patients' social-cognitive functions. Social-cognitive neuroscience is a nascent research discipline that has only emerged within the last decade, providing a framework for systematic studies on social cognition in different neurological and psychiatric disorders.

Social cognition, the building block of social behavior, refers to any processing that is elicited by, about, and directed towards other people (Kirsch, 2006; Kennedy & Adolphs, 2012). Although the term social cognition encompasses a broad range of different mental processes (Lieberman, 2007; Adolphs, 2009; Kennedy & Adolphs, 2012), they are often grouped into two broad categories: those associated with automatic bottom-up processing that are mainly driven by internal and external stimuli, and those associated with controlled top-down processing that are mainly driven by personal and contextual factors (Lieberman, 2007; Adolphs, 2009). These bottom-up and top-down processes include the *rapid identification* of social stimuli such as the recognition of people through different sensory channels, the corresponding *generation* and *perception* of *internal psychophysical responses*, the *understanding* and *interpretation* of the perceived social stimuli, and the subsequent *generation* and *execution* of an appropriate response (Kirsch, 2006; Adolphs, 2009). Overall, converging evidence from neuroimaging studies in healthy populations and human lesion studies shows that these bottom-up and top-down processes are mediated predominantly by fronto-temporal and also parietal brain regions

(Gallagher & Frith, 2003; Saxe & Powell, 2006; Lieberman, 2007; Adolphs, 2009; Scholz, Triantafyllou, Whitfield-Gabrieli, Brown, & Saxe, 2009). While limbic regions, including the mesial temporal lobe, are known to be critical for automatic bottom-up processing of social stimuli, frontal lobe regions function to modulate these processes via top-down control (Lieberman, 2007; Adolphs, 2009; Ray & Zald, 2012).

The role of the amygdala in social cognition has been studied most extensively with respect to the perception of facial emotional expressions. In this regard, numerous neuroimaging and lesion studies in humans demonstrate that the amygdala is a key region for the recognition of particularly negatively valenced facial expressions, most consistently shown for fear (e.g., Adolphs et al., 1994; Breiter et al., 1996; Morris et al., 1996; Whalen et al., 1998; Adolphs, Tranel, et al., 1999). The involvement of the amygdala in the recognition of emotional prosody appears to be less prominent, with few existing studies showing preserved recognition of emotional prosody despite focal bilateral amygdala damage due to UWD (Adolphs & Tranel, 1999; Bach, Hurlemann, & Dolan, 2013; Meletti et al., 2014). Based on more recent evidence (Seeley et al., 2007; Craig, 2009; Pessoa, 2010), the amygdala is currently acknowledged to be significantly involved in the detection of internal and extrapersonal stimuli that are homeostatically relevant to the organism, a process referred to as salience processing (Seeley et al., 2007; Menon & Uddin, 2010). Consequently, the rapid identification of stimuli that are salient to the organism, because they are either unpredictable, associated with reward or punishment, or signal important information, involves the amygdala (Seeley et al., 2007; Adolphs, 2009; Craig, 2009). In this regard, the region is responsible for the generation of an emotional response to any kind of salient stimulus such as the perception of a facial emotional expression. Due to the reciprocal connections between the amygdala and different regions of the brainstem (LeDoux, 1996; Price, 1999; Cardinal et al., 2002), the amygdala also contributes to the generation of physiological responses that are associated with salient events. This dual role the amygdala in the processing of salience and the coordination of appropriate physiological responses is consistent with early theories of emotion (James, 1884; Lange, 1885) and current models of human awareness (Craig, 2009) and empathy (Singer, Critchley, & Preuschoff, 2009), suggesting that interoceptive information from the body is essential for both self-related and empathic feeling states.

The anterior insula (AI) is another region that has been intimately linked to salience processing and that has attracted enormous attention in the field of social-cognitive neuroscience. Emerging evidence shows that the AI is a key node of an intrinsic “salience network” that also includes the amygdala and that integrates highly processed sensory stimuli with interoceptive information from the body (Seeley et al., 2007; Menon & Uddin, 2010). The AI has been demonstrated to be implicated in a broad variety of different tasks that engage people’s awareness, including decision making, time perception, and heartbeat awareness (Craig, 2009). Therefore, the region is now considered as the substrate of human awareness that sequentially integrates homeostatic conditions with the sensory environment and with motivational, hedonic, and social conditions represented in other parts of the brain (Craig, 2002, 2003, 2009). Both neuroimaging and lesion studies in humans have more recently shown that the AI is critical for the awareness of not only self-related but also of empathic feelings states (Singer et al., 2004; Bernhardt & Singer, 2012; Gu et al., 2012; Leigh et al., 2013). Consequently, the AI significantly contributes to the awareness of emotional and physiological reactions to salient cues and to the understanding and interpretation of other people’s minds (Craig, 2002; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Singer et al., 2004; Craig, 2009).

Another important process of social cognition that helps humans understand other people’s mind and that has been extensively investigated in the field of social-cognitive neuroscience is theory of mind (ToM). ToM refers to the ability to infer mental states such as beliefs, intentions, and feelings from others (Frith & Frith, 2003). At the neuronal level, ToM reasoning has been linked predominantly to frontal and lateral temporal regions, including the medial prefrontal cortex, the superior temporal sulcus, the temporal pole, and also to the adjacent temporoparietal junction (Frith & Frith, 2006; Saxe, 2006; Saxe & Baron-Cohen, 2006). More recent evidence suggests that cognitive (intentions, beliefs) and affective (feelings) mental state attributions are functionally and neuroanatomically dissociable, with the amygdala involved primarily in affective rather than cognitive ToM (Abu-Akel & Shamay-Tsoory, 2011).

In summary, it is evident that the amygdala plays a key role for different bottom-up and top-down processes of social cognition. The region is particularly involved in the automatic generation of emotional and psychophysiological responses to social stimuli. In this way, the amygdala influences the top-down processes of response generation and execution that are

mediated by regions of the frontal lobe. Consequently, the amygdala is rightly considered a key structure within the “social” brain (Kennedy & Adolphs, 2012), which highlights the negative impact of disorders associated with amygdala lesions on patients’ social cognition and social behavior. Together with converging evidence showing that social-cognitive functions are a crucial mediator of people’s psychological health (Helliwell & Putnam, 2004; Sherman et al., 2008), the presence of mesial temporal lobe damage in patients with MTLE emphasizes the relevance and need for studies on social cognition in this patient population.

Various interictal behavioral changes in patients with MTLE were recognized early on and have become known as Waxman–Geschwind Syndrome (Waxman & Geschwind, 1975; Bear & Fedio, 1977). Interestingly, Waxman and Geschwind (1975) have already conceptualized peculiar symptoms such as hypergraphia, changes in sexual behavior, and aggressiveness as manifestations of fronto-limbic lesions. However, only the recent emergence of social-cognitive neuroscience has provided a theoretical and methodological framework to systematically investigate the impact of brain damage associated with MTLE on social cognition. Based on the involvement of the mesial temporal lobe in the recognition of facial (Adolphs et al., 1994; Adolphs, Tranel, et al., 1999) and prosodic emotions (Scott et al., 1997; Adolphs & Tranel, 1999), various recent studies have investigated basic facial and prosodic emotion recognition in MTLE.

Overall, the findings demonstrate that MTLE is specifically associated with impaired recognition of facial and prosodic emotions (Meletti et al., 2003; Benuzzi et al., 2004; McClelland et al., 2006; Hlobil, Rathore, Alexander, Sarma, & Radhakrishnan, 2008; Meletti et al., 2009; Bonora et al., 2011; Broicher, Kuchukhidze, et al., 2012; Sedda et al., 2013; Tanaka et al., 2013; Meletti et al., 2014). In line with the particular role of the amygdala for the processing of negative emotions, especially of fear, converging evidence shows that MTLE affects predominantly the recognition of negative basic emotions, including fear, disgust, sadness, and anger (Meletti et al., 2003; Meletti et al., 2009; Broicher, Kuchukhidze, et al., 2012; Sedda et al., 2013; Tanaka et al., 2013). In summary, these studies demonstrate that patients with early-onset bilateral and right MTLE are most affected, which supports previous evidence on the predominance of the right hemisphere for the processing of negative emotions (Adolphs, Damasio, Tranel, & Damasio, 1996; Borod et al., 1998; Craig, 2005).

Because MTLE affects the mesial temporal lobe and also remote frontal and lateral temporal regions that are involved in ToM reasoning, a growing number of studies have investigated ToM in patients with MTLE (Shaw et al., 2004; Schacher, Winkler, et al., 2006; Giovagnoli et al., 2011; Broicher, Kuchukhidze, et al., 2012; Giovagnoli, Parente, Villani, Franceschetti, & Spreafico, 2013; Li et al., 2013; Hennion et al., 2014). These studies have consistently shown that particularly early-onset MTLE is a specific risk factor for the development of ToM deficits, regardless of whether ToM was measured by verbal or non-verbal tasks. However, in contrast to facial emotion recognition, the severity of ToM deficits has been shown to be independent from the laterality of unilateral MTLE. This finding is in line with the high association of ToM with top-down functions of the frontal lobe, particularly with cognitive perspective-taking abilities, which are suggested to be more bilaterally represented in the brain than the processing of negative emotions (Craig, 2005; Carrington & Bailey, 2009). Moreover, a recent study was the first to show that left MTLE is specifically associated with social inference deficits that included difficulties with the comprehension of paralinguistic cues displayed during social interactions (Cohn, St-Laurent, Barnett, & McAndrews, 2014). Despite the evidence for gender-related differences in material-specific cognitive functions (Helmstaedter, 1999; Helmstaedter, Brosch, et al., 2004), the studies on emotion recognition and ToM have not reported an impact of gender, neither with regard to the general population of MTLE nor with regard to the lateralization of MTLE (Meletti et al., 2009; Giovagnoli et al., 2011; Broicher, Kuchukhidze, et al., 2012; Hennion et al., 2014).

Given the strong link between the amygdala and fear, previous fMRI studies have used static and dynamic as well as implicit and explicit fearful faces to investigate the functional integrity of the amygdala and its connections in patients with MTLE (Benuzzi et al., 2004; Batut et al., 2006; Schacher, Haemmerle, et al., 2006; Bonelli et al., 2009; Broicher et al., 2010; Broicher, Frings, et al., 2012; Labudda, Mertens, Steinkroege, Bien, & Woermann, 2013). The majority of these studies have demonstrated that unilateral MTLE is associated with decreased brain responses to fearful faces, predominantly affecting regions of the ipsilesional mesial temporal lobe, including the amygdala, and widespread regions of the cortex. Importantly and in agreement with the findings on facial emotion recognition, RMTLE has been found to be accompanied by a more widespread pattern of hypoactivation than LMTLE (Benuzzi et al., 2004;

Batut et al., 2006; Broicher, Frings, et al., 2012; Labudda et al., 2013). These findings have led to the suggestion that, depending on the lesion side, unilateral MTLE asymmetrically affects both the behavioral and neuronal processing of fearful facial expressions.

In summary, research on social cognition in patients with MTLE has demonstrated that particularly early-onset bilateral and right MTLE are specifically associated with deficits in social cognition, affecting basic processes such as facial and prosodic emotion recognition and more complex processes such as ToM and the comprehension of paralinguistic social cues (e.g., Meletti et al., 2003; Meletti et al., 2009; Broicher, Kuchukhidze, et al., 2012; Cohn et al., 2014). In line with the findings on episodic memory, these deficits are at least partly attributable to structural and functional brain changes and cannot merely be explained by other epilepsy-related factors, including antiepileptic medication and psychiatric comorbidities (Figure 2, p. 16). Moreover, MTLE affects not only emotion recognition that depends highly upon the integrity of the mesial temporal lobes but also affects ToM and social inference abilities that rely more on frontal and lateral temporal regions than on the mesial temporal lobes. The correspondence between the etiopathogenesis of “classic” cognitive and social-cognitive impairments demonstrates that the cognitive profiles of MTLE patients are significantly determined by brain abnormalities within and outside the epileptogenic mesial temporal lobes. Importantly, consistent evidence shows that an early-onset of MTLE is associated with increased severity of cognitive impairments showing that early brain damage due to MTLE interferes with plastic reorganization processes and the normal development of cognition.

While social-cognitive neuroscience is a growing discipline within the field of epilepsy, little is yet known about the neuronal correlates of social-cognitive impairments in MTLE. Firstly, although brain damage in MTLE affects anatomically remote fronto-temporal regions that overlap with regions required for normal social cognition, previous neuroimaging studies on social cognition have focused mainly on the mesial temporal lobe, particularly on the amygdala. Secondly, these studies have almost exclusively concentrated on functional rather than structural brain changes. Finally, despite the view of the amygdala as the “controller of the brainstem”, previous research has neglected to investigate how MTLE affects remote brainstem regions during the processing of social information. However, such knowledge on the neuronal correlates is essential to better understand the nature of impaired social cognition in MTLE and

to develop appropriate diagnostic and treatment approaches targeting these difficulties (Szemere & Jokeit, 2015).

1.3 Urbach-Wiethe disease

In contrast to the relatively common disorder of MTLE, UWD (Urbach & Wiethe, 1929) is a very rare genetic recessive disorder, with less than 300 cases reported since its first clear description in 1929 (Hamada et al., 2002). UWD, also known as lipid proteinosis or hyalinosis cutis et mucosae, is characterized by both dermatological and neurological symptoms (Hamada et al., 2002). The dermatological symptoms vary greatly among cases but often include hoarseness of voice that frequently starts from birth or infancy, lesions and scarring on the skin, and beading of the papules around the eyelids (Desmet et al., 2005). These symptoms are the consequence of a general thickening of the skin and the membranes, which are caused by mutations in the extracellular matrix protein 1 gene (ECM1) located on chromosome 1q21 (Hamada et al., 2002). Although the dermatological changes are the most classic and typically earliest symptoms of UWD, 50-75% of patients demonstrate selective calcifications of the bilateral mesial temporal lobe, most commonly of the amygdala (Newton, Rosenberg, Lampert, & O'Brien, 1971; Staut & Naidich, 1998). These calcifications, which start at an early age and progress with increasing disease duration, are the result of a buildup of calcium deposits and a subsequent hardening of the surrounding blood vessels, a process that causes progressive brain damage (Appenzeller et al., 2006). Because UWD is frequently associated with mesial temporal lobe damage, the disease can be complicated by MTLE (Newton et al., 1971) and by psychiatric comorbidities, including depression, anxiety, and psychotic symptoms (Thornton et al., 2008). Although UWD patients are found worldwide, a comparatively high prevalence of diagnoses (about 25% of the total population of less than 300 cases) have been reported in South Africa (Heyl, 1970; Van Houghenouck-Tulleken et al., 2004). This comparatively high occurrence of UWD in South Africa is probably attributable to the founder effect⁴. Currently, there is no cure available for UWD, but many of the dermatological and neurological symptoms can be individually treated to increase the quality of life of affected patients.

⁴ The term founder effect is used in population genetics and refers to the loss of genetic variation occurring when a new population is established by a very small number of individuals from a larger population.

In contrast to MTLE, previous research on neurobehavioral comorbidities in UWD is comparatively scarce and involves two major methodological limitations that reduce the extent to which the findings can be generalized. Firstly, because of the very low incidence of the disease, the majority of studies investigating such comorbidities included only a few cases. Secondly, the psychiatric and cognitive profiles differ markedly between patients (Thornton et al., 2008; Becker et al., 2012), which is consistent with the variation in the extent and progression of amygdala damage among UWD cases. Nevertheless, due to the occurrence of selective bilateral amygdala damage in a high portion of patients, UWD has provided a unique lesion model to study the impact of circumscribed amygdala lesions on memory, social-cognitive, and psychophysiological processing. So far, the effect of focal bilateral amygdala damage on UWD patients' cognition has been most extensively studied with regard to emotional memory and fear processing. As the present thesis does not involve research on the "classic" cognitive functions in UWD, the following section includes only a brief overview on the most common findings.

1.3.1 "Classic" cognitive functions

Consistent with the key role of the amygdala in enhancing declarative memory for emotional material, the most striking deficits among the "classic" cognitive functions in UWD is impaired emotional memory (Markowitsch et al., 1994; Adolphs et al., 1997; Siebert, Markowitsch, & Bartel, 2003; Hurlemann et al., 2007). As expected due to the bilateral mesial temporal lobe damage, impaired verbal and non-verbal episodic memory for neutral material has also been reported (Thornton et al., 2008). However, the "classic" cognitive deficits in UWD are not restricted to the domain of episodic memory but may also affect executive and generalized cognitive functions (Thornton et al., 2008). This finding is consistent with the cognitive profiles of patients with MTLE and may at least partly be caused by impaired acquisition of higher-order cognitive functions due to affective abnormalities and by deafferentation of remote regions due to bilateral mesial temporal lobe damage.

1.3.2 *Social-cognitive functions*

Much of our current understanding on human fear processing stems from rare cases with focal bilateral amygdala damage due to UWD, which has played a key role in establishing the historical conceptualization of the amygdala as a fear module (Öhman & Mineka, 2001). There is a consistent line of work showing that UWD cases with focal bilateral amygdala damage are impaired on the recognition of facial emotional expressions, particularly of fear, disgust, anger, and sadness (Adolphs et al., 1994; Adolphs, Tranel, Damasio, & Damasio, 1995; Calder, 1996; Adolphs, Russell, & Tranel, 1999; Adolphs & Tranel, 1999; Adolphs, Tranel, et al., 1999; Siebert et al., 2003; Thornton et al., 2008). This finding that UWD affects the recognition of particularly negative facial expressions is consistent with the facial emotion recognition deficits found in patients with MTLE. However, in contrast to patients with MTLE, the few studies on prosodic emotion recognition in cases of UWD have shown preserved recognition of emotional prosody (Adolphs & Tranel, 1999; Bach et al., 2013; Meletti et al., 2014).

The most consistent evidence comes from a series of investigations in a unique female case, known as patient SM, suffering from circumscribed and complete bilateral amygdala damage. These case studies have shown that the patient is remarkably impaired on different aspects of social cognition, including the recognition of fearful facial expressions (Adolphs et al., 1994) and the ability to accurately judge faces of unfamiliar people (Adolphs, Tranel, & Damasio, 1998; Adolphs & Tranel, 2000). It has also been shown that SM is missing some of the deepest negative emotions from past experiences, in a manner that parallels her deficit in perceiving such emotions (Tranel et al., 2006). More recently, the patient has been found to display an absence of overt fear manifestations and an overall impoverished experience of fear (Feinstein, Adolphs, Damasio, & Tranel, 2011; Feinstein et al., 2013).

A few prior studies have investigated the impact of incomplete bilateral amygdala damage on fear-related autonomic responses. Consistent with the top-down control of the amygdala on autonomic brainstem regions (LeDoux, 1996; Price, 1999; Cardinal et al., 2002), some evidence suggests that UWD is associated with diminished fear-related physiological responses (Bechara et al., 1995; Becker et al., 2012; Klumpers, Morgan, Terburg, Stein, & van Honk, 2014). However, other evidence indicates that UWD involves preserved modulation of physiological responses to internally and externally triggered fear (Becker et al., 2012; Feinstein et al., 2013).

Importantly, previous research has shown that the presence and the degree of fear-related behavioral and autonomic impairments vary greatly from case to case (Adolphs, Russell, et al., 1999; Adolphs, Tranel, et al., 1999; Becker et al., 2012), which may be attributable to interindividual differences in age at lesion onset, extent of amygdala damage, presence of epilepsy, and genetic and environmental influences. Surprisingly, even identical twin sisters with focal damage largely circumscribed to the BLA have been found to differ on the presence and the degree of fear-related impairments (Becker et al., 2012; Mihov et al., 2013). Based on this observation, subsequent studies have examined the potential occurrence of functional compensation, with preliminary evidence showing that the presence or absence of functional compensation within (Terburg et al., 2012) and outside (Becker et al., 2012; Mihov et al., 2013) the amygdala may contribute to such interindividual differences in fear-related processing.

Despite the high interindividual variability within the population of UWD, the overall picture shows that UWD is associated with impaired fear processing, which affects facial emotion recognition, fear experience, fear conditioning, and fear-related autonomic responses. So far, the impact of bilateral amygdala damage on social-cognitive processing in UWD has been mainly studied at the behavioral level. The low number of fMRI studies investigating social cognition in UWD can be explained by the rarity of the disease that results in a lack of statistical power required for fMRI group comparisons. Consequently, in order to properly investigate the neuronal correlates of impaired social cognition in UWD, neuroimaging methods and protocols are required that are applicable at the individual level.

2 Thesis objectives

Based on the preceding literature review, it is evident that episodic memory has been extensively investigated in patients with MTLE. Although MTLE is often difficult to treat with AEDs, epilepsy surgery is a successful treatment option for a large proportion of patients. One major risk of unilateral mesial temporal lobe resections is a material-specific decline of anterograde episodic memory. Visual-spatial navigation fMRI helps clinicians determine the lateralization of unilateral MTLE and assess the risk for postsurgical memory loss in a broad spectrum of MTLE patients, including children, the elderly, and individuals with mental handicaps. However, in the absence of visual memory as in congenitally blind patients with MTLE, it is unknown whether nonvisual spatial navigation can sufficiently activate the mesial temporal lobes for individual memory lateralization. This scientific question is of high clinical relevance as blind patients are particularly reliant on intact memory.

Consequently, the first key objective of the present thesis was to investigate the diagnostic value of nonvisual spatial navigation fMRI in an extraordinary patient with medically refractory unilateral MTLE and accompanying congenital blindness.

The recent emergence of social-cognitive neuroscience has clearly demonstrated that MTLE is not only associated with episodic memory impairments but is also a specific risk factor for the development of deficits in basic and complex processes of social cognition, including facial and prosodic emotion recognition, ToM, and the understanding of paralinguistic social cues. So far, these social-cognitive impairments have been attributed to functional abnormalities predominantly in the mesial temporal lobe and also in widespread regions of the cortex. However, previous research has not directly examined whether MTLE affects the function of remote cortical and subcortical regions that are essential for normal social cognition.

Therefore, the second key objective was to study the impact of unilateral MTLE on the function of anatomically remote but interconnected cortical and subcortical regions during the processing of social information.

Consistent evidence shows that MTLE is associated not only with functional abnormalities within and outside the mesial temporal lobes but also with structural damage in widespread

regions of the temporal and frontal lobes that are involved in social cognition. Nevertheless, previous research has focused mainly on the functional rather than on the structural correlates of social-cognitive deficits frequently observed in patients with MTLE.

Therefore, the third key objective was to study the structural correlates of impaired social cognition in unilateral MTLE.

Previous research on UWD has demonstrated remarkable interindividual differences in the presence of fear-related impairments. One factor that may account for such interindividual variability is residual or compensatory activity within and outside the amygdala. However, to properly investigate this research question in this extremely rare patient population, neuroimaging protocols are required that are applicable at the single-subject level. In addition, because of the inconsistent findings on fear-related autonomic processing in UWD, more studies are needed to gain further insight into the consequences of bilateral amygdala damage on autonomic functions of the brainstem.

Consequently, the fourth key objective was to investigate the presence or absence of residual or compensatory activation within the amygdala of two UWD cases with incomplete bilateral amygdala damage. Moreover, the impact of incomplete bilateral amygdala damage on psychophysiological functions was examined. To account for potential interindividual differences, research methodologies were used that are valid at the single-subject level.

The first publication contains the study on nonvisual spatial navigation fMRI in an extraordinary patient with unilateral MTLE and concurrent congenital blindness. The second publication includes the investigation of the impact of unilateral MTLE on remote cortical and subcortical brain regions that are crucial for empathic feelings of fear. The third publication contains the study on the structural correlates of empathy in unilateral MTLE. The fourth publication involves the preliminary findings on the impact of incomplete bilateral amygdala damage due to UWD on the neuronal and psychophysiological responses to fearful faces.

3 Research publications (peer-reviewed)

1. Toller G, Adhimoolam B, Grunwald T, Huppertz HJ, König K, Jokeit H. Nonvisual spatial navigation lateralizes mesial temporal lobe epilepsy in a patient with congenital blindness. *Neurocase*, 2014.
2. Toller G, Adhimoolam B, Grunwald T, Huppertz HJ, Kurthen M, Rankin K, Jokeit H. Right mesial temporal lobe epilepsy impairs empathy-related brain responses to dynamic fearful faces. *Journal of Neurology*, 2015.
3. Toller G, Adhimoolam B, Rankin KP, Huppertz HJ, Kurthen M, Jokeit H. Right fronto-limbic atrophy is associated with reduced empathy in refractory unilateral mesial temporal lobe epilepsy. *Neuropsychologia*, 2015.
4. Toller G, Ives-Deliperi V, Butler J, Rauch L, Evans R, Jokeit H. Amygdala dysfunction with preserved psychophysiological and subjective arousal in two patients with Urbach-Wiethe disease. Submitted.

3.1 Nonvisual spatial navigation lateralizes mesial temporal lobe epilepsy in a patient with congenital blindness

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Abstract

Nonvisual spatial navigation fMRI may help clinicians determine memory lateralization in blind individuals with refractory MTLE. We report on an exceptional case of a congenitally blind woman with late-onset left MTLE undergoing presurgical memory fMRI. To activate mesial temporal structures despite the lack of visual memory, the patient was requested to recall familiar routes using nonvisual multisensory and verbal cues. Our findings demonstrate the diagnostic value of a nonvisual fMRI task to lateralize MTLE despite congenital blindness and may therefore contribute to the risk assessment for postsurgical amnesia in rare cases with refractory MTLE and accompanying congenital blindness.

Keywords: mesial temporal lobe epilepsy; congenital blindness; spatial navigation fMRI; memory

Introduction

Spatial navigation functional magnetic resonance imaging (fMRI) provides a useful method to lateralize mesial temporal lobe epilepsy (MTLE) and to assess the risk for memory loss associated with anterior temporal lobe resection (Jokeit, Okujava, & Woermann, 2001; Janszky et al., 2005; Avila et al., 2006; Schacher et al., 2006). The paradigm's clinical benefit has been clearly demonstrated in a broad spectrum of MTLE patients including children, elderly, and individuals with mental handicaps. However, in the absence of visual memory as in the case of refractory MTLE and accompanying congenital blindness, it is unknown whether nonvisual spatial navigation can sufficiently activate mesial temporal regions for individual memory lateralization.

The congenital lack of visual input causes extensive functional reorganization of the brain, with the deprived visual cortices being activated by inputs from nonvisual sensory and verbal modalities (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Kupers et al., 2006). Consistently, both animal and human studies provide converging evidence that the ability to represent spatial information and to navigate independently in space is relatively well preserved in light-deprived animals and congenitally blind individuals (Save, Cressant, Thinus-Blanc, & Poucet, 1998; Fortin et al., 2008; Kupers, Chebat, Madsen, Paulson, & Ptito, 2010). In addition, congenitally blind and sighted subjects have recently been shown to recruit a strikingly similar functional network when navigating in space that included mesial temporal regions involved in spatial cognition and memory (Kupers et al., 2010; Halko, Connors, Sánchez, & Merabet, 2014). These findings have led to the suggestion that owing to the adaptive functional reorganization of brain regions mediating nonvisual sensory and verbal modalities, individuals with congenital blindness are able to form spatial representations despite their lack of visual experience (Cattaneo et al., 2008; Struiksma, Noordzij, & Postma, 2009).

Therefore, it is reasonable to assume that nonvisual spatial navigation would also be an appropriate method to functionally map mesial temporal regions in individuals with MTLE and concurrent congenital blindness. Here, we report on an extraordinary case of a congenitally blind woman with refractory MTLE undergoing memory fMRI during comprehensive presurgical evaluation.

Methods

Clinical history

We studied a 45-year-old woman with congenital blindness diagnosed at the age of 4 months based on the following clinical features: amaurosis, absent electroretinogram and visual evoked potentials, and absent pupillary responses. At that time, the profound blindness was demonstrated to be caused by retinal degeneration and optical nerve atrophy. Our neurological examination during comprehensive presurgical evaluation reconfirmed the patient's amaurosis. The right-handed (assessed by the Edinburgh Handedness Inventory; Oldfield, 1971) woman was a proficient Braille reader, walked independently using a guide dog, had three children, and worked as a skilled social worker. At the age of 42, she developed refractory epilepsy. High-resolution MRI over the next 2 years demonstrated an unchanged left-sided amygdala enlargement (Figure 1A/B, p. 40). The underlying etiology remained unknown until the study was finished. Seizure semiology, continuous ictal/interictal video-EEG monitoring, and neuropsychological findings were concordant with the structural MRI, confirming the diagnosis of left MTLE. At the time of fMRI, the patient was treated with lamotrigine 25 mg/day and levetiracetam 3000 mg/day; she had approximately two seizures per day and reported increasing verbal memory impairment. Due to the significantly reduced seizure frequency following a subsequent therapy with lamotrigine 200 mg/day and levetiracetam 2750 mg/day, further presurgical evaluations were temporarily ceased by the patient.

Nonvisual spatial navigation fMRI

Experimental paradigm

Roland's Hometown Walking task (Roland, Eriksson, Stone-Elander, & Widen, 1987) was used to induce memory-related activity within the mesial temporal lobe, as has been previously demonstrated in sighted individuals with and without MTLE (Jokeit et al., 2001; Janszky et al., 2005; Schacher et al., 2006). The spatial navigation paradigm typically used with sighted subjects was adapted. Based on previous evidence for cross-modal plasticity in congenitally blind individuals, the patient was instructed to mentally navigate through 10 different familiar routes by focusing on nonvisual sensory (haptic, auditory, gustatory, and olfactory) and linguistic (verbal and semantic) cues (Cattaneo et al., 2008; Struiksma et al., 2009). The

paradigm included 20 alternating activation and baseline (simple counting task) blocks, each lasting 30 s.

Image acquisition

Structural and functional images were acquired on a 3.0-T Philips scanner using a 32-channel head coil. A T1-weighted 3D magnetization prepared rapid gradient echo sequence was used to obtain the structural image (176 sagittal slices, 1-mm thick, skip = 0 mm; repetition time = 8.1 ms; echo time = 3.7 ms; flip angle = 8°; field of view = 240 x 240 mm²; voxel size = 1 mm³; matrix size = 256 x 256). The functional images were obtained using a gradient echo planar imaging sequence (repetition time = 3000 ms; echo time = 35 ms; flip angle = 75°; field of view = 220 x 220 mm²; voxel size = 2.75 x 2.75 x 4 mm; matrix size = 128 x 128). Thirty-two coronal slices (4-mm thick, skip = 0 mm) were acquired orthogonal to the hippocampus and covered the temporal and frontal lobes.

Image preprocessing and analyses

Functional imaging data were analyzed using BrainVoyager QX software (Brain Innovation, Maastricht, The Netherlands; Goebel, Esposito, & Formisano, 2006). The subject's T1 image was transformed into Talairach space. The functional images were slice-time corrected, realigned, co-registered to the normalized T1 image and re-sampled at a voxel size of 3 mm³. To remove low-frequency drifts, high pass temporal filtering with a low cut-off of three cycles per run was applied. The contrast image navigation > counting was calculated. To address our a priori hypothesis that nonvisual spatial navigation would activate regions involved in episodic memory, two functional regions of interest (ROIs) were extracted from the right (hippocampus, parahippocampal gyrus) and left (hippocampus, parahippocampal gyrus) mesial temporal lobe. To quantify the ratio of activated voxels between the two functional ROIs, a lateralization index (LI; right-left/right+left) was computed on the thresholded t-map ($P_{\text{FWE}} < .005$; $k = 5$). The caudal border of the ROIs was set at the crus of the fornix (Jokeit et al., 2001; Janszky et al., 2005; Schacher et al., 2006).

Language fMRI and verbal cognition

Based on the fMRI parameters described in the previous section, verbal fluency was used to determine language dominance (Woermann et al., 2003). The German versions of the Wechsler Adult Intelligence Scale (verbal subtests; Von Aster, Neubauer, & Horn, 2006) and the Rey Auditory Verbal Learning Test (Helmstaedter, Lendt, & Lux, 2001) were administered.

Results

Nonvisual spatial navigation fMRI

Consistent with the presence of left MTLE, the left ROI consisted only of parahippocampal activation, whereas the right ROI included activation in parahippocampal gyrus and anterior hippocampus. The comparison of the number of significant voxels between the contralesional and ipsilesional ROI showed an LI = .30 outside the range previously reported in healthy controls (Schacher et al., 2006), reflecting an asymmetric right-sided activation of the mesial temporal lobes (Figure 1C/D, p. 40). The overall activity pattern in extra-mesial temporal regions showed a left hemisphere predominance that was accompanied by a right-sided co-activation of the cerebellum (Table 1, p. 39). Bilateral dorsolateral prefrontal and secondary motor cortices as well as bilateral inferior temporal and fusiform gyri were activated. Left-lateralized activity was found in middle temporal and inferior frontal gyri, pre-SMA, brainstem, and anterior cingulate cortex.

Language fMRI and verbal cognition

Left hemisphere language dominance was established (Figure 1E/F, p. 40). The patient's level of verbal cognitive functioning fell within the normal range (IQ = 89). By contrast, learning ($z = -1.83$), retention ($z = -2.76$), and recall ($z = -2.57$) of the 15-item word list were impaired.

Discussion

This study is, to the best of our knowledge, the first fMRI case report on nonvisual spatial navigation in a presurgical patient with unilateral MTLE and concurrent congenital blindness. In line with previous research in sighted MTLE patients and congenitally blind individuals without MTLE (Jokeit et al., 2001; Janszky et al., 2005; Avila et al., 2006; Schacher et al., 2006; Kupers et

al., 2010; Halko et al., 2014), the present findings clearly show that nonvisual spatial navigation is suitable for mapping mesial temporal regions despite the co-occurrence of MTLE and congenital blindness. The recall of spatial episodic memories was associated with a rightward asymmetry of the mesial temporal lobes, referring to the presence of functional deficits adjacent to the epileptogenic lesion. In the presence of left hemisphere language dominance, this pattern of results is supported by the subjectively reported and the neuropsychologically measured verbal memory impairment suggesting that the contralateral mesial temporal lobe is not sufficient to fully compensate for left mesial temporal dysfunction. Overall, the current findings indicate that our blind patient with late-onset MTLE is not at increased risk for amnesia following left amygdalo-hippocampectomy but for a gradual decline in verbal episodic memory (Helmstaedter, Brosch, Kurthen, & Elger, 2004; Janszky et al., 2005).

Besides this predominant involvement of the right mesial temporal lobe, the neuronal response elicited by nonvisual spatial navigation included the bilateral fusiform gyrus, a region also known to underlie spatial cognition (Maguire, Frackowiak, & Frith, 1997). In addition, language-related (inferior frontal and middle temporal gyri, pre-SMA, cerebellum), secondary motor, and visual association (inferior temporal gyrus) areas were activated. Consistent with previous research on spatial cognition and navigation in both sighted and congenitally blind individuals (Cattaneo et al., 2008; Struiksma et al., 2009; Kupers et al., 2010; Halko et al., 2014), this activity pattern strongly suggests that the patient recruited linguistic, motor, and nonvisual sensory sources during spatial navigation.

Overall, our findings clearly indicate that the blind MTLE patient recalled spatial memories by relying on nonvisual modalities and therefore support previous evidence that spatial imagery and cognition is not modality-specific (Cattaneo et al., 2008; Struiksma et al., 2009). In addition, the present results demonstrate the clinical value of a nonvisual spatial navigation task to lateralize MTLE despite co-occurring blindness. Therefore, this case study suggests that blind individuals with refractory MTLE may benefit from spatial memory fMRI in terms of risk assessment of postsurgical amnesia — a meaningful finding for the clinical diagnostics and therapy of this specific patient group particularly reliant on intact memory. To ultimately confirm the validity of the methodological approach applied to our blind patient with MTLE,

both subjective and neuropsychological assessments of postsurgical episodic memory performance would be required.

Acknowledgments

The authors acknowledge Dr. Dominik Huber and Thekla Kaisen for technical assistance during fMRI acquisition, and Dr. Victoria Reed for the final edits of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Swiss Epilepsy Foundation.

Table 1. Activity pattern elicited by the nonvisual recall of familiar routes in a congenitally blind patient with left MTLE.

Anatomic region	L/R	Cluster size	Talairach coordinates			t-score
			x	y	z	
Middle frontal gyrus (BA 9)	R	621	41	19	27	11.42
Cerebellum	R	1492	17	-47	-43	11.03
Middle temporal gyrus	L	906	-46	-23	-15	10.90
Fusiform gyrus	L	945	-31	-23	-33	10.11
Parahippocampal gyrus	L	†				
Superior frontal gyrus (BA 6)	R	204	23	-8	51	9.84
Middle frontal gyrus (BA 6)	L	1759	-37	-2	51	9.79
Parahippocampal gyrus	R	480	20	-14	-27	9.40
Hippocampus	R	†				
Superior frontal gyrus (BA 6)	L	184	-22	1	63	9.32
Pre-SMA	L	412	-10	7	45	8.43
Inferior temporal gyrus	R	569	44	-35	-27	8.40
Fusiform gyrus	R	†				
Inferior frontal gyrus (BA 44/45)	L	139	-49	13	6	8.37
Middle frontal gyrus (BA 9)	L	865	-28	31	36	8.28
Brainstem (tectum)	L	167	-1	-23	-9	7.46
Anterior cingulate cortex	L	244	-7	16	42	7.45
Inferior temporal gyrus	L	185	-55	-29	-30	7.29

Talairach coordinates given for maximum *t*-score for each cluster. Results are significant at $P_{FWE} < .005$, $k = 5$. L = left; R = right. †Regions included in the cluster immediately above.

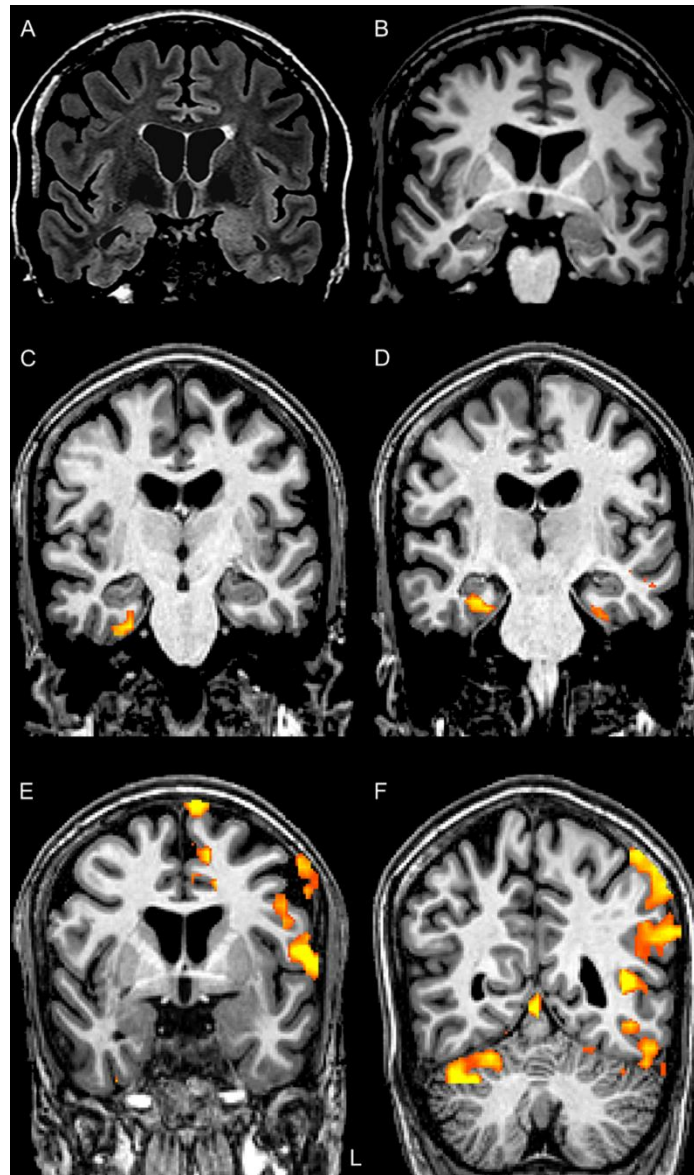


Figure 1. Structural and functional MRI data. (A) Coronal fluid-attenuated inversion recovery image shows minimal hyperintensity in the left amygdala. (B) Corresponding volume increase on T1-weighted image. (C/D) Rightward asymmetry of the mesial temporal lobes (C, $y = -11$; D, $y = -15$) during nonvisual spatial navigation versus counting. Left-lateralized activation of (E) anterior ($y = -1$) and (F) posterior ($y = -45$) language areas, and (F) right-lateralized activation of the cerebellum ($y = -45$) during word generation versus rest. For both the memory and language task, the normalized functional images are displayed at $P_{\text{FWE}} < .005$, $k = 5$ and are superimposed on the subject's normalized structural image. Coordinates refer to Talairach space. L = left.

References

- Amedi, A., Raz, N., Pianka, P., Malach, R., & Zohary, E. (2003). Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. *Nature Neuroscience*, 6, 758-766.
- Avila, C., Barros-Loscertales, A., Forn, C., Mallo, R., Parcet, M. A., Belloch, V., . . . Gonzalez-Darder, J. M. (2006). Memory lateralization with 2 functional MR imaging tasks in patients with lesions in the temporal lobe. *AJNR American Journal of Neuroradiology*, 27, 498-503.
- Cattaneo, Z., Vecchi, T., Cornoldi, C., Mammarella, I., Bonino, D., Ricciardi, E., & Pietrini, P. (2008). Imagery and spatial processes in blindness and visual impairment. *Neuroscience and Biobehavioral Reviews*, 32, 1346-1360.
- Fortin, M., Voss, P., Lord, C., Lassonde, M., Pruessner, J., Saint-Amour, D., . . . Lepore, F. (2008). Wayfinding in the blind: Larger hippocampal volume and supranormal spatial navigation. *Brain*, 131, 2995-3005.
- Goebel, R., Esposito, F., & Formisano, E. (2006). Analysis of functional image analysis contest (FIAC) data with Brainvoyager QX: from single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Human Brain Mapping*, 27, 392-401.
- Halko, M. A., Connors, E. C., Sánchez, J., & Merabet, L. B. (2014). Real world navigation independence in the early blind correlates with differential brain activity associated with virtual navigation. *Human Brain Mapping*, 35, 2768-2778.
- Helmstaedter, C., Brosch, T., Kurthen, M., & Elger, C. E. (2004). The impact of sex and language dominance on material-specific memory before and after left temporal lobe surgery. *Brain*, 127, 1518-1525.
- Helmstaedter, C., Lendt, M., & Lux, S. (2001). *VLMT: Verbaler Lern-und Merkfähigkeitstest*. Göttingen: Beltz Test GmbH.
- Janszky, J., Jokeit, H., Kontopoulou, K., Mertens, M., Ebner, A., Pohlmann-Eden, B., & Woermann, F. G. (2005). Functional MRI predicts memory performance after right mesiotemporal epilepsy surgery. *Epilepsia*, 46, 244-250.
- Jokeit, H., Okujava, M., & Woermann, F. G. (2001). Memory fMRI lateralizes temporal lobe epilepsy. *Neurology*, 57, 1786-1793.

- Kupers, R., Chebat, D. R., Madsen, K. H., Paulson, O. B., & Ptito, M. (2010). Neural correlates of virtual route recognition in congenital blindness. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 12716-12721.
- Kupers, R., Fumal, A., de Noordhout, A. M., Gjedde, A., Schoenen, J., & Ptito, M. (2006). Transcranial magnetic stimulation of the visual cortex induces somatotopically organized qualia in blind subjects. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 13256-13260.
- Maguire, E. A., Frackowiak, R. S., & Frith, C. D. (1997). Recalling routes around London: activation of the right hippocampus in taxi drivers. *The Journal of Neuroscience*, *17*, 7103-7110.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*, 97-113.
- Roland, P. E., Eriksson, L., Stone-Elander, S., & Widen, L. (1987). Does mental activity change the oxidative metabolism of the brain? *The Journal of Neuroscience*, *7*, 2373-2389.
- Save, E., Cressant, A., Thinus-Blanc, C., & Poucet, B. (1998). Spatial firing of hippocampal place cells in blind rats. *The Journal of Neuroscience*, *18*, 1818-1826.
- Schacher, M., Haemmerle, B., Woermann, F. G., Okujava, M., Huber, D., Grunwald, T., . . . Jokeit, H. (2006). Amygdala fMRI lateralizes temporal lobe epilepsy. *Neurology*, *66*, 81-87.
- Struiksma, M. E., Noordzij, M. L., & Postma, A. (2009). What is the link between language and spatial images? Behavioral and neural findings in blind and sighted individuals. *Acta Psychologica*, *132*, 145-156.
- Von Aster, M., Neubauer, A., & Horn, R. (2006). *Wechsler Intelligenztest für Erwachsene (WIE). Deutschsprachige Bearbeitung und Adaptation des WAIS-III von David Wechsler*. Frankfurt am Main: Harcourt Test Services.
- Woermann, F. G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., . . . Ebner, A. (2003). Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology*, *61*, 699-701.

3.2 Right mesial temporal lobe epilepsy impairs empathy-related brain responses to dynamic fearful faces

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Abstract

Unilateral mesial temporal lobe epilepsy (MTLE) has been associated with reduced amygdala responsiveness to fearful faces. However, the effect of unilateral MTLE on empathy-related brain responses in extra-amygdalar regions has not been investigated. Using functional magnetic resonance imaging, we measured empathy-related brain responses to dynamic fearful faces in 34 patients with unilateral MTLE (18 right-sided), in an epilepsy (extra-MTLE; $n = 16$) and in a healthy control group ($n = 30$). The primary finding was that right MTLE (RMTLE) was associated with decreased activity predominantly in the right amygdala and also in bilateral periaqueductal gray (PAG) but normal activity in the right anterior insula. The results of the extra-MTLE group demonstrate that these reduced amygdala and PAG responses go beyond attenuation caused by antiepileptic and antidepressant medication. These findings clearly indicate that RMTLE affects the function of mesial temporal and midbrain structures that mediate basic interoceptive input necessary for the emotional awareness of empathic experiences of fear. Together with the decreased empathic concern found in the RMTLE group, this study provides neurobehavioral evidence that patients with RMTLE are at increased risk for reduced empathy towards others' internal states and sheds new light on the nature of social-cognitive impairments frequently accompanying MTLE.

Key words: mesial temporal lobe epilepsy, fMRI, fearful faces, empathy

Introduction

Mesial temporal lobe epilepsy (MTLE) is the most frequent focal epilepsy and is often difficult to treat with antiepileptic drugs. Consistent with the well-established literature on interictal behavioral changes in MTLE (Waxman & Geschwind, 1975), more recent studies have shown that unilateral MTLE is also associated with impaired social cognition affecting the recognition of facial and prosodic emotions (Meletti et al., 2003; Meletti et al., 2009; Bonora et al., 2011; Broicher, Kuchukhidze, et al., 2012) as well as the understanding of other people's intentions and beliefs (Schacher, Winkler, et al., 2006; Giovagnoli et al., 2011; Broicher et al., 2012).

Empathy, the ability to share the feelings of others, provides another crucial capacity for successful social interaction (Eisenberg & Strayer, 1990; Preston & De Waal, 2002). Although a consensus on its precise definition is yet to be reached, there is broad agreement that empathy involves an emotional response as well as the cognitive processes of perspective-taking and self–other distinction. This cascade of affective and cognitive processes allows individuals to infer others' emotional states by generating an isomorphic affective state while recognizing that the initiating agent of this subjective emotional experience is the counterpart and not the self (Eisenberg & Strayer, 1990; Preston & De Waal, 2002; Singer et al., 2004; Shamay-Tsoory et al., 2005; Decety & Lamm, 2006; Singer, 2006; Shamay-Tsoory, 2011).

Following the seminal article of Preston and De Waal (2002) suggesting that firsthand and vicarious experiences of affective states are partially based on shared neuronal representations, subsequent functional imaging studies have consistently supported the shared network hypothesis of empathy for a variety of states including pain (Singer et al., 2004; Saarela et al., 2007; Lamm, Decety, & Singer, 2011), disgust (Wicker et al., 2003), anger (de Greck et al., 2012), and fear (de Gelder, Snyder, Greve, Gerard, & Hadjikhani, 2004). Overlapping activity between self- and other-oriented body and feeling states have most consistently been found in the anterior insula (AI) — a finding that has led to the suggestion that the AI provides a substrate for the emotional awareness of not only self-related but also of empathic feeling states (Craig, 2002; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Singer et al., 2004; Craig, 2009; Singer, Critchley, & Preuschoff, 2009). This dual function of the AI has been confirmed by recent lesion studies showing that empathy is reduced in patients with AI damage (Gu et al., 2012;

Leigh et al., 2013). Moreover, an emotional asymmetry of the left and right AI has been demonstrated, with the left AI primarily involved in cognitive-evaluative forms of empathy and group-oriented (affiliative) emotions, and the right AI mainly engaged in affective-perceptual forms of empathy and individual-oriented (survival) emotions (Craig, 2005; Fan, Duncan, de Greck, & Northoff, 2011; Lamm et al., 2011).

One emotion that is highly related to survival is fear. The affective response to a fear-eliciting stimulus has been clearly shown to rely predominantly on the amygdala (Adolphs, Tranel, Damasio, & Damasio, 1994; LeDoux, 1996; Adolphs et al., 1999). Consistent with the shared network hypothesis of empathy, increased amygdala activity has been found when healthy subjects observed either static fearful faces (Breiter et al., 1996; Morris et al., 1996) or fear expressed by the entire body (de Gelder et al., 2004). Moreover, the autonomic and behavioral responses associated with self-related feelings of fear have been demonstrated to be mediated by the reciprocal connections between the amygdala and midbrain periaqueductal gray (PAG) (Davis, 1992; Price, 1999; Cardinal, Parkinson, Hall, & Everitt, 2002). Consistently, activity in both the amygdala and PAG has been found in healthy subjects during the experience of intense fear (Mobbs et al., 2009; Mobbs et al., 2010). Based on the proposed dual function of the AI for the emotional awareness of self- and other-related feeling states (Critchley et al., 2004; Craig, 2009; Singer et al., 2009), the interoceptive information processed in the amygdala and PAG is integrated in the AI and thus provides a fundamental basis for the emotional awareness of both firsthand and empathic experiences of fear.

In line with the presence of mesial temporal damage, unilateral MTLE has been particularly associated with decreased ipsilesional amygdala responses to either static or dynamic fearful faces (Benuzzi et al., 2004; Batut et al., 2006; Schacher, Haemmerle, et al., 2006; Bonelli et al., 2009; Broicher, Frings, et al., 2012; Labudda, Mertens, Steinkroege, Bien, & Woermann, 2013). Consistent with the neuronal representation of negative facial expressions (Adolphs, Damasio, Tranel, & Damasio, 1996; Borod et al., 1998), predominantly right MTLE (RMTLE) has been shown to be accompanied by extra-mesial hypoactivation, affecting widely distributed cortical regions involved in fearful face processing (Benuzzi et al., 2004; Labudda et al., 2013). These findings have been supported by a recent study showing that RMTLE is associated with reduced fear intensity ratings of dynamic fearful faces (Labudda et al., 2013). However, despite the

evidence that the amygdala, PAG, and AI mediate the emotional response of self- and other-related fear and in spite of the functional connections between the amygdala and both the PAG (LeDoux, 1996) and AI (Seeley et al., 2007; Tomasi & Volkow, 2011), previous research has primarily focused on mesial temporal structures and has not directly examined whether unilateral MTLE affects empathy-related brain responses in the PAG and AI to fearful faces.

Therefore, in the present study, we aimed to investigate whether unilateral MTLE is associated with altered amygdala, PAG, and AI activity during the observation of fearful faces. We used functional magnetic resonance imaging (fMRI) and an affective-perceptual task that involved the presentation of dynamic fearful faces and that was previously validated in both healthy controls and patients with unilateral MTLE (Schacher, Haemmerle, et al., 2006; Broicher et al., 2012). Based on the results of the healthy control group, functional regions of interest (ROIs) were derived from the amygdala, PAG, and AI for group comparisons. To investigate whether unilateral MTLE is specifically associated with reduced empathy-related brain responses to fearful faces and to control for potential attenuation of BOLD activity caused by antiepileptic (Jokeit, Okujava, & Woermann, 2001; Kida, Smith, Blumenfeld, Behar, & Hyder, 2006) and antidepressant (Windischberger et al., 2010) medication, an epilepsy control group consisting of patients with extra-mesial temporal lesions and seizure onsets (extra-MTLE) was included. Because of the affective-perceptual fMRI task we used, self-reports of empathic concern and personal distress were additionally measured and correlated with activity in the functional ROIs. Our primary hypothesis was that patients with RMTLE in particular would show reduced empathy-related brain activity in the amygdala, PAG, and AI that would not merely be attributable to BOLD signal attenuation caused by antiepileptic and antidepressant medication.

Methods

Participants

A total of 80 participants (30 healthy controls, 16 patients with left MTLE (LMTLE), 18 with RMTLE, and 16 with extra-MTLE) were included in the present study. Thirty-four out of 59 patients with medically refractory unilateral MTLE, undergoing comprehensive presurgical evaluation at the Swiss Epilepsy Center Zurich, were recruited between 2007 and 2013. All MTLE patients fulfilled the following diagnostic criteria: unilateral hippocampal sclerosis (HS)

demonstrated by axial and coronal T1- and T2-weighted high-resolution MR images; unilateral seizure onset of temporal origin shown by continuous interictal and ictal video-EEG monitoring with scalp and intracranial (18%) electrodes; concordance between the side of HS and the side of seizure onset; no bilateral HS; no additional brain pathologies; and valid fMRI. The extra-MTLE group consisted of patients with lesions and seizure onsets in frontal, temporo-lateral, parietal, and occipital lobes. Inclusion criteria for the extra-MTLE group required a diagnosis of drug-resistant localization-related epilepsy (non-lesional = 31%; lesional = 69%), confirmed by a neurological examination, continuous interictal and ictal video-EEG monitoring with scalp and intracranial (25%) electrodes, and structural MRI. Extra-MTLE patients with multiple pathologies on MRI were excluded (for detailed clinical information see supplementary Table 1, p. 74). Due to the relatively high prevalence of affective disorders in epilepsy patients (for a review see Kanner et al., 2012), mild to moderate depressive symptoms identified by psychiatric interviews were not exclusion criteria. At the time of fMRI scanning, all patients were treated with antiepileptic drugs (AEDs) either as mono- (LMTLE = 31%; RMTLE = 39%; extra-MTLE = 38%) or polytherapy (LMTLE = 69%; RMTLE = 61%; extra-MTLE = 63%). Eleven patients were on antidepressant treatment (see supplementary Table 2, pp. 75-77, for detailed information on each patient's antiepileptic and, if used, antidepressant treatment). Except for levetiracetam, the three epilepsy groups did not differ on the number of patients treated with any of the antiepileptic and antidepressant substances used across groups (supplementary Table 2, pp. 75-77). Based on clinical histories and structural MRI, all healthy controls were free of current or previous neurological or psychiatric disorders, alcohol or substance abuse, and chemotherapy. Except for age, the diagnostic groups were matched with respect to all demographic and clinical variables (Table 1, p. 60).

Empathy questionnaire

The subjects completed the Saarbruecker Personality Questionnaire (SPF; Paulus, 2009), an adapted and psychometrically validated German version of the Interpersonal Reactivity Index (IRI; Davis, 1983), within 12 months of the fMRI scanning. The 16-item SPF is a self-report questionnaire composed of four subscales that evaluate both affective and cognitive aspects of empathy (Paulus, 2009). Because of the affective perceptual fMRI task used in the present

study, we included only the two subscales that measure the affective aspects of empathy: Empathic Concern (EC: the other-oriented feelings elicited by another's emotional state) and Personal Distress (PD: the self-oriented feelings of anxiety and discomfort in tense interpersonal situations), with scores ranging from 4 to 20 for each subscale. While higher EC scores represent a more developed capacity for empathizing, higher PD scores are negatively related to measures of overall social functioning. Due to the heterogeneity of either lesion foci or seizure onsets in the extra-MTLE group (see supplementary Table 1, p. 74), the SPF was administered only to healthy controls and patients with unilateral MTLE. Because only German-speaking subjects with normal intelligence (regular schooling) and intact reading comprehension completed the questionnaire, the sample sizes included in the behavioral data analyses differed from the sample sizes included in the functional imaging analyses (see Table 2, p. 60, for demographic and clinical information for the SPF groups).

Statistical analyses

The subsamples of the healthy control, LMTLE, and RMTLE groups (Table 2, p. 60) did not differ in their proportions of men and women [$\chi^2(2, 50) = .4; P > .05$], but differed significantly in age [$H(2, 50) = 6.1; P < .05$] and the presence of depressive symptoms [$\chi^2(2, 50) = 12.9; P < .01$]. As each subject's SPF raw scores were transformed into age-adjusted norm values (<http://bildungswissenschaften.uni-saarland.de>), age was not included as a covariate in the following analyses. Separate one-way (group: healthy controls, LMTLE, RMTLE) analyses of covariance (controlling for depressive symptoms) were conducted on both EC and PD subscales. Significant main effects were analyzed post hoc using false discovery rate (FDR) correction for multiple comparisons (Benjamini & Yekutieli, 2001).

Functional imaging

Fearful face paradigm

The fMRI task used in this study was previously validated in both healthy controls and patients with unilateral MTLE (Schacher, Haemmerle, et al., 2006). In brief, the paradigm consisted of 16 alternating activation and baseline blocks each lasting 24 seconds. During the activation conditions, a total of 75 brief (2-3 seconds) episodes selected from thriller and horror

movies were presented. All episodes showed faces of actors expressing intense fear, but no violence or aggression. During the baseline conditions, 72 short video recordings of local landscapes were shown. The stimuli were presented on a screen using a projector and were viewed through an overhead mirror. The participants were told that they would see brief episodes of dynamic fearful faces alternating with landscape scenes. They were instructed to relax and to focus on the actors' eyes.

Image acquisition

Structural and functional MRI scans were acquired on a 3.0-T scanner (Philips Medical Systems, Best, The Netherlands) using a 32-channel head coil. A T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) sequence was used to obtain the structural images (176 sagittal slices, 1-mm thick, skip = 0 mm; repetition time = 8.1 ms; echo time = 3.7 ms; flip angle = 8°; field of view = 240 x 240 mm²; voxel size = 1 mm³; matrix size = 256 x 256). The functional scans were obtained using a gradient echo planar imaging sequence (repetition time = 1500 ms; echo time = 35 ms; flip angle = 75°; field of view = 220 x 220 mm²; voxel size = 2.75 x 2.75 x 4 mm; matrix size = 128 x 128). Eighteen coronal slices (4-mm thick, skip = 0 mm) were acquired orthogonal to the hippocampal formation and were spread over the temporal lobe. Foam padding was used to reduce head motion.

Image preprocessing and analyses

Functional imaging data were analyzed using Statistical Parametric Mapping (SPM)8 (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007). After discarding the first 16 volumes to allow for magnetic field stabilization, functional images were realigned, co-registered, normalized to the MNI template and re-sampled at a voxel size of 2 mm³, and smoothed with a 4mm full-width at half-maximum Gaussian kernel. To remove low-frequency drifts, high pass temporal filtering with a cut-off of 128 s was applied. To create regressors of interest, each subject's time series of both conditions (fearful faces/landscapes) were modelled by SPM8's canonical hemodynamic response function, with each participant's six estimated motion parameters included as regressors of no interest. For each participant, contrast images were calculated by applying the contrast fearful faces > landscapes to the parameter estimates. To

detect regional BOLD signal changes associated with fearful face processing within each diagnostic group, one-sample *t*-tests were performed. Age was included as a nuisance covariate to account for potential within-group differences in fearful face processing caused by different age ranges (St Jacques, Bessette-Symons, & Cabeza, 2009; Mather, 2012). Two-sample *t*-tests were used to generate group difference maps among control, LMTLE, RMTLE, and extra-MTLE, with age as a confounding covariate to control for between-group differences in age (Table 1, p. 60). A peak threshold of $P_{FWE} < .05$ and an extent threshold of four contiguous voxels (2 x 2 x 2 mm) were applied to the contrasts within the healthy controls and to all between-group contrasts. Because an overall attenuation of BOLD activity was found in all three patient groups, the contrasts within each epilepsy group were thresholded at $P < .0001$, uncorrected, $k = 4$.

To improve statistical power for group comparisons and to address our a priori hypotheses, ROI analyses were conducted using MarsBaR (Brett, Anton, Valabregue, & Poline, 2002). To obtain task-specific functional ROIs, corresponding peak MNI coordinates were derived from the FWE-corrected contrast map (fearful faces > landscapes) of the healthy controls (Table 3, pp. 61-62). The ROIs were centered on the right (24, -10, -12; 30, -4, -22) and left (-34, -8, -22; -16 -8 -14) amygdala, the right (8, -30, -6) and left (-4, -30, -6) PAG, and the right AI (44, 22, -2). None of the patients with extra-MTLE had structural lesions within any of the selected ROIs. For each diagnostic group, mean contrast values were extracted within 2-mm spherical volumes centered on the above maxima. To compare the groups with respect to their mean activity within each ROI, two sample *t*-tests were conducted, with age included as a nuisance covariate. A statistical threshold of $P < .05$, Bonferroni-corrected for the number of ROIs included (Brett et al., 2002), was used for all ROI analyses.

Relationship between empathy-related brain responses and measures of affective empathy

To test whether the empathy-related brain responses in the amygdala, PAG, and AI were related to self-reported affective empathy, the mean BOLD signal changes extracted from each ROI were correlated with the empathic concern and personal distress raw scores obtained across groups (healthy controls, $n = 29$; LMTLE, $n = 9$; RMTLE, $n = 12$; Table 2, p. 60). As for the behavioral analyses, age and the presence of depressive symptoms were included as nuisance

covariates. The correlational analyses were thresholded at $P < .05$, corrected for the number of ROIs included.

Results

Demographic and clinical data

Demographic and clinical data are presented in Table 1, p. 60. Group differences were found only in age. The three epilepsy groups did not differ with respect to age at epilepsy onset, duration of epilepsy, presence of depressive symptoms, and antiepileptic and antidepressant medication ($P > .05$).

Empathy questionnaire

The main effect of group was found on both the empathic concern [EC; $F(2, 50) = 4.0$; $P < .05$] and personal distress [PD; $F(2, 50) = 10.9$; $P < .001$] subscales (Figure 1, p. 64). Post-hoc pairwise comparisons demonstrated that the RMTLE patients reported significantly lower EC than both the healthy controls ($P < .05$, FDR-corrected) and the LMTLE patients ($P < .05$, FDR-corrected). The EC scores of the LMTLE and healthy control groups did not differ from each other ($P > .05$). The PD scores obtained in the healthy control group were significantly lower compared with the LMTLE ($P < .01$, FDR-corrected) and RMTLE ($P < .001$, FDR-corrected) groups. The difference between the LMTLE and RMTLE patients on the PD subscale was not significant ($P > .05$).

Functional imaging

Within-group results

The contrast fearful faces > landscapes demonstrated distinct activity patterns within diagnostic groups (Table 3, pp. 61-62). In the healthy controls, regional increases in BOLD activity were found in mesial temporal lobe (amygdala, hippocampus) and midbrain (PAG) bilaterally, with a lateralization to the right in the precentral gyrus, superior temporal gyrus, inferior frontal gyrus, putamen, and AI ($P_{\text{FWE}} < .05$). In the LMTLE patients, significant clusters were shown in bilateral mesial temporal lobe (contralateral amygdala, bilateral hippocampus) and bilateral midbrain (right red nucleus, left PAG), with right-sided activations yielded in the

putamen, inferior frontal gyrus, precentral gyrus, middle temporal gyrus, AI, and superior temporal gyrus ($P < .0001$, uncorrected). By contrast, in the RMTLE group, significant clusters were found only in the right AI and thalamus bilaterally ($P < .0001$, uncorrected). Consistent with the structural integrity of mesial temporal regions in the extra-MTLE group, significant BOLD increases were confined to the right amygdala, right midbrain (tectum), and left hippocampus ($P < .0001$, uncorrected). Figure 2 (p. 65) displays mean activity in the midbrain, mesial temporal lobe, and AI within diagnostic groups.

Between-group results

Except for the group contrast healthy controls > RMTLE, none of the group comparisons revealed any clusters that survived correction for multiple comparisons ($P_{FWE} > .05$). Compared to the healthy controls, the RMTLE patients showed decreased activity in a small cluster ($k = 8$) including the right amygdala and hippocampus (MNI peak, 24, -10, -14; $T = 5.71$; $P_{FWE} < .05$).

ROI results

According to two sample t -tests restricted to the ROIs in bilateral amygdala and bilateral PAG, and the right AI, the healthy controls showed greater activity than the LMTLE patients in bilateral amygdala and the right PAG, with the largest difference in the left amygdala ($P < .05$, corrected; Table 4, p. 63). None of the ROIs were more activated in the LMTLE group ($P > .05$, corrected). Compared to the healthy controls, decreased BOLD activity was found in bilateral amygdala and PAG of the RMTLE group ($P < .05$, corrected). The ROIs centered on the right amygdala were the regions that differed most between the healthy controls and the patients with RMTLE. The inverse contrast (healthy controls < RMTLE) yielded no activity differences ($P > .05$, corrected). The BOLD signal in the right amygdala of the RMTLE patients was reduced compared to both the healthy controls and the LMTLE patients ($P < .05$, corrected). No differences were found between the healthy controls and the patients with extra-MTLE; except for one ROI in the right amygdala (24, -10, -12) that was less activated in the extra-MTLE group. None of the remaining group contrasts (LMTLE > extra-MTLE; LMTLE < extra-MTLE; RMTLE > extra-MTLE; RMTLE < extra-MTLE) were significant ($P > .05$, corrected).

Correlation results of empathy-related brain responses and measures of affective empathy

Linear regression analysis across groups (healthy controls, $n = 29$; LMTLE, $n = 9$; RMTLE, $n = 12$; Table 2, p. 60) showed that mean activity in the right amygdala (ROI center: 24, -10, -12) was positively correlated with self-reported empathic concern (EC; $r = 0.39$, $P < .05$, corrected) (Figure 3, p. 66). None of the inverse correlations reached significance ($P > .05$, corrected). No relationship was found between the personal distress scores and mean activity in any of the ROIs ($P > .05$, corrected).

Discussion

The main goal of the present study was to investigate whether unilateral MTLE is associated with altered empathy-related brain responses in the amygdala, PAG, and AI during the observation of dynamic fearful faces. Consistent with our hypothesis, the primary finding was that RMTLE was accompanied by a widespread pattern of hypoactivation that included decreased activity mainly in the right amygdala and also in bilateral PAG. Surprisingly, activity in the right AI was not different in the RMTLE patients than in the other diagnostic groups. In the LMTLE group, however, we found a strikingly similar network to that seen in the healthy controls with reduced responses shown particularly in the left amygdala and also in the right PAG. The similar activation in bilateral amygdala, bilateral PAG, and the right AI found between the extra-MTLE and healthy control groups demonstrates that RMTLE in particular is specifically associated with decreased empathy-related brain responses to dynamic fearful faces that go beyond attenuation caused by antiepileptic and antidepressant medication. Consistent with the decreased amygdala and PAG responses observed in the RMTLE group, their empathic concern scores were lower compared to both the healthy controls and the LMTLE patients. We further found a positive association between the right amygdala activity and self-reported empathic concern across the healthy control, LMTLE, and RMTLE groups, which provides additional evidence that patients with RMTLE are at increased risk for reduced empathy towards others' internal states.

Consistent with evidence on the brain regions that mediate firsthand feelings of fear (Mobbs et al., 2009; Mobbs et al., 2010) and the shared network hypothesis of empathy (Gallese, 2001; Preston & De Waal, 2002; Singer et al., 2009), the overall right-sided activity

pattern recruited in the healthy controls included bilateral amygdala, bilateral PAG, and the right AI. Increased activity was further found in regions involved in action and motion perception (precentral and inferior frontal gyri, superior temporal gyrus) that have probably been evoked by the dynamic nature of the stimulus material used in the present study. The right hemisphere predominance of the network that involved the strongest activity in the right amygdala and a right-lateralized activity in the AI supports previous evidence showing that self- and other-related negative emotions are represented primarily in the right hemisphere (Adolphs et al., 1996; Borod et al., 1998; Craig, 2005).

Similarly, the activity pattern of the LMTLE patients showed a right hemisphere asymmetry that included the right amygdala, left PAG, and right AI, with the strongest response found in the right amygdala. In line with these results, the ROI analyses revealed that activity predominantly in the left amygdala and also in the right PAG of the LMTLE patients was decreased compared to the healthy controls, with no activity differences found in the left PAG and right AI. In contrast to the healthy controls and the LMTLE patients, the cortical and subcortical brain responses within the group of RMTLE patients were strongly decreased including hypoactivation found in bilateral amygdala and bilateral PAG. Consistent with the presence of right mesial temporal damage, the whole-brain group comparison between the RMTLE and healthy control groups revealed decreased activity in the right amygdala of the RMTLE patients. These findings were supported by the ROI analyses indicating that the RMTLE group showed lower activity primarily in the right amygdala than both the healthy controls and the LMTLE patients, and decreased activity in bilateral PAG when compared to the healthy controls. Despite this reduced neuronal responsiveness to dynamic fearful faces that has been partly demonstrated in previous studies (Schacher, Haemmerle, et al., 2006; Broicher, Frings, et al., 2012; Labudda et al., 2013), the RMTLE group showed the strongest activity in the right AI that did not differ from the other diagnostic groups. Because the two MTLE groups were matched with regard to demographic and clinical parameters, the asymmetric impact of right and left MTLE on the empathy-related brain responses is highly likely to represent a specific effect of lesion side. Consistent with the structural integrity of the mesial temporal lobes in the extra-MTLE group, increased activity was found mainly in the right amygdala and left hippocampus, with the strongest response revealed in the right amygdala.

The high responsiveness of the right amygdala that was found not only in the healthy controls but also in the LMTLE and extra-MTLE groups and the strong hypoactivation in the right amygdala of the RMTLE patients provide concurrent evidence for the crucial role of the right amygdala for vicarious experiences of fear. This consistent pattern of results was supported by the low empathic concern scores shown in the RMTLE group and the positive association we found between right amygdala activity and empathic concern reported across the healthy control, LMTLE and RMTLE groups. Importantly, the decreased empathic concern scores we found in the RMTLE patients compared to the healthy control and the LMTLE groups cannot be attributed to between-group differences in comorbid depressive symptoms, which is particularly remarkable considering that their self-ratings may be positively biased due to poor insight associated with their right-hemispheric lesion. These findings are in agreement with preceding studies showing that RMTLE is accompanied by impaired recognition of negative facial emotions (Meletti et al., 2003; Benuzzi et al., 2004; McClelland et al., 2006; Hlobil, Rathore, Alexander, Sarma, & Radhakrishnan, 2008; Meletti et al., 2009; Sedda et al., 2013) and confirm the association previously demonstrated between right amygdala damage and reduced affective empathy (Hillis, 2013; Leigh et al., 2013). The decreased amygdala responsiveness to dynamic fearful faces and the higher personal distress scores we found in both MTLE groups compared to the healthy controls appear to be contradictory findings (Lamm, Batson, & Decety, 2007). However, as the healthy controls reported very low levels of personal distress, the personal distress scores may have been biased by socially desirable responding. For these reasons, the group differences found on self-reported personal distress should be interpreted with caution.

Consistent with the reciprocal connections between the amygdala and PAG (LeDoux, 1996), the present study is the first to show that unilateral MTLE, and especially right-sided MTLE, is associated with decreased PAG responses to dynamic fearful faces. Notably, the comparable PAG activation in the healthy controls and the extra-MTLE patients demonstrates that MTLE is specifically related to decreased PAG activity that goes beyond attenuation caused by antiepileptic and antidepressant medication. Based on the involvement of the PAG in autonomic fear responses in the self (LeDoux, 1996) and the crucial role of internal bodily states for firsthand and empathic feeling states (Craig, 2009; Singer et al., 2009), these results indicate

that RMTLE in particular involves a reduced autonomic brain response to dynamic fearful faces. These findings are corroborated by preceding evidence demonstrating an association between MTLE and interictal autonomic dysfunction (Druschky et al., 2001; Ansakorpi et al., 2002). However, as we did not evaluate autonomic functions during fearful face processing, the correspondence between PAG activity and patients' autonomic responses to fearful faces needs to be investigated in future studies. It is of note that we did not detect differences in PAG activity between the three patient groups, which is probably attributable to medication-associated BOLD decreases across groups (Jokeit et al., 2001; Kida et al., 2006), and a high within-group variability in BOLD signal intensities caused by different disease-related factors including medication, brain morphology, and disease duration.

Surprisingly, despite the functional connections between the amygdala and AI (Seeley et al., 2007; Tomasi & Volkow, 2011) and in spite of the widespread pattern of hypoactivation found in the RMTLE group, the empathy-related brain responses in the right AI were comparable among all diagnostic groups. In conjunction with the finding of thalamic activity observed only in the RMTLE group, these results suggest that the RMTLE patients recruited a thalamo-insular pathway (Seeley et al., 2007) that may reflect either a compensatory or a disinhibitory effect associated with the right mesial temporal lesion. Based on the proposed dual function of the AI for the emotional awareness of both firsthand and empathic feeling states (Craig, 2003, 2009; Singer et al., 2009), the present findings indicate that the cortical re-representation and integration of interoceptive information involved in vicarious experiences of fear is unaffected by both right and left MTLE. However, the reduced empathy-related brain responses in the amygdala and PAG found mainly in the RMTLE group demonstrate that RMTLE is associated with altered interoceptive input to the AI during the observation of fearful faces. Consequently, these findings suggest that RMTLE is accompanied by a reduced emotional response to fear observed in others, which is consistent with previous data showing that MTLE patients reported difficulties with the identification of their own emotions (Broicher et al., 2012). Given that an emotional response constitutes an essential component for the full-blown experience of empathy (Decety & Lamm, 2006), our findings indicate that patients with RMTLE are at increased risk for reduced empathy for other people's feelings of fear, which supports recent

evidence showing an association between RMTLE and reduced intensity ratings of dynamic fearful faces (Labudda et al., 2013).

Taken together, the present findings are the first to show that unilateral MTLE, and in particular right-sided MTLE, is specifically associated with decreased empathy-related brain responses in the amygdala and PAG but normal responses in the right AI during the observation of dynamic fearful faces. These results show that RMTLE affects not the function of the cortical region that mediates the emotional awareness of vicarious experiences of fear, but the function of mesial temporal and midbrain structures that provide basic interoceptive input for such conscious empathic feelings of fear. These findings are consistent with the decreased empathic concern reported by the RMTLE group and the positive association we found between self-reported empathic concern and activity in the right amygdala across groups. Consequently, we provide neurobehavioral evidence that patients with RMTLE are at increased risk for reduced empathy towards internal states of others — a finding that is consistent with and complements research on patients with neurodegenerative disease (Rankin et al., 2006; Sturm et al., 2013) and stroke (Hillis, 2013; Leigh et al., 2013).

The present results elucidate early neuropsychiatric concepts on specific interictal behavioral changes in patients with MTLE (Waxman & Geschwind, 1975), and may offer new insights in terms of etiopathogenesis, diagnosis, and treatment of impaired social cognition and affective processing associated with MTLE. In this way, the current study contributes to the neuroscientific and clinical understanding of social interactions, and thus to one of the key factors for subjective well-being and quality of life in patients with MTLE (Sherman et al., 2008).

Acknowledgments

The authors acknowledge Dr. Dominik Huber and Thekla Kaisen for technical assistance during fMRI acquisition, and Dr. Victoria Reed for the final edits of the manuscript. This work was supported by the Swiss Epilepsy Foundation.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical standards

All patients and controls provided written informed consent. The study was approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Table 1. Demographic and clinical information for each diagnostic group.

Demographic and clinical variables	Group				Statistics	<i>P</i>
	Controls (<i>n</i> =30)	LMTLE (<i>n</i> =16)	RMTLE (<i>n</i> =18)	extra-MTLE (<i>n</i> =16)		
Sex, % female	56.7	56.3	50.0	50.0	$\chi^2(3) = .3$.953
Age, mean years (<i>SD</i>)	38.2 (12.4)	33.0 (12.9)	43.6 (11.5)	29.5 (13.4)	$F(3) = 4.2$.008
Language dominance ^a , % atypical	3.3	6.3	16.7	25.0	$\chi^2(3) = 5.8$.120
Age at epilepsy onset, median years (range)	—	11.0 (2-34)	12.0 (1-44)	10.5 (3-27)	$H(2) = .2$.919
Duration of epilepsy, median years (range)	—	18.5 (2-47)	24.5 (4-51)	14.5 (2-40)	$H(2) = 3.7$.160
AEDs ^b , median <i>n</i> per day (range)	—	2.0 (1-3)	1.0 (1-3)	2.0 (1-3)	$H(2) = 5.4$.069
Depressive symptoms, % <i>n</i>	—	37.5	38.9	37.5	$\chi^2(2) = .0$.995
Antidepressants, % <i>n</i>	—	31.3	16.7	18.8	$\chi^2(2) = 1.2$.550

^a Language dominance was determined using a verbal fluency task (Woermann et al., 2003); ^b AEDs, antiepileptic drugs.

Table 2. Demographic and clinical information for the SPF groups.

Demographic and clinical variables	Group			Statistics	<i>P</i>
	Controls (<i>n</i> =29)	LMTLE (<i>n</i> =9)	RMTLE (<i>n</i> =12)		
Sex, % female	55.2	66.7	58.3	$\chi^2(2) = .4$.830
Age, median years (range)	35.6 (22-63)	26.5 (15-53)	47.4 (27-61)	$H(2) = 6.1$.048
Language dominance ^a , % atypical	3.4	11.1	16.7	$\chi^2(2) = 2.2$.340
Age at epilepsy onset, mean years (<i>SD</i>)	—	14.2 (9.6)	19.8 (16.4)	$t(18) = -1.0$.345
Duration of epilepsy, mean years (<i>SD</i>)	—	16.6 (15.3)	25.1 (13.6)	$t(19) = -1.4$.193
AEDs ^b , median <i>n</i> per day (range)	—	2.0 (1-3)	1.0 (1-2)	$U = 36.0$.150
Depressive symptoms, % <i>n</i>	—	22.2	41.7	$\chi^2(1) = .9$.350
Antidepressants, % <i>n</i>	—	11.1	25.0	$\chi^2(1) = .6$.422

^a Language dominance was determined using a verbal fluency task (Woermann et al., 2003); ^b AEDs, antiepileptic drugs.

Table 3. Activity patterns elicited by dynamic fearful faces within each diagnostic group.

Anatomic region	L/R	Cluster size	MNI coordinates			t-score
			x	y	z	
<i>Healthy controls</i>						
Amygdala (LB)	R	279	24	-10	-12	12.00
Amygdala (LB)	R	†	30	-4	-22	
Hippocampus	R	†	34	-18	-8	
Hippocampus	L	300	-24	-14	-12	8.85
Amygdala (LB)	L	†	-34	-8	-22	
Amygdala (SF)	L	†	-16	-8	-14	
Precentral gyrus (BA 6)	R	75	54	10	34	8.33
Midbrain (PAG)	R	32	8	-30	-6	8.19
Midbrain (Substantia nigra)	L	10	-10	-22	-10	8.02
Superior temporal gyrus	R	46	56	-20	-6	7.97
Midbrain (PAG)	L	6	-4	-30	-6	6.99
Inferior frontal gyrus (BA 45)	R	60	54	22	24	6.94
Putamen	R	13	24	0	10	6.69
Anterior insula	R	39	44	22	-2	6.40
<i>LMTLE patients</i>						
Amygdala (LB)	R	107	30	-4	-14	8.96
Hippocampus	R	†	34	-12	-14	
Amygdala (SF)	R	†	22	-8	-12	
Hippocampus	L	33	-18	-12	-16	8.12
Midbrain (red nucleus)	R	9	8	-24	-12	6.27
Putamen	R	5	22	2	8	6.03
Midbrain (PAG)	L	4	-4	-32	-6	5.97
Inferior frontal gyrus (BA 45)	R	4	52	24	-4	5.93
Precentral gyrus (BA 6)	R	45	46	6	44	5.89
Inferior frontal gyrus (BA 44)	R	6	54	18	34	5.71

Research publications

Anatomic region	L/R	Cluster size	MNI coordinates			<i>t</i> -score
			x	y	z	
Middle temporal gyrus	R	5	50	-26	-14	5.55
Anterior insula	R	4	44	22	0	5.49
Superior temporal gyrus	R	6	54	-12	-6	5.40
<i>RMTLE patients</i>						
Anterior insula	R	19	38	18	-2	9.20
Thalamus	L	11	-14	-28	-6	7.57
Thalamus	R	12	12	-30	-2	6.56
<i>Extra-MTLE patients</i>						
Amygdala (LB)	R	12	28	-6	-14	7.10
Midbrain (tectum)	R	8	12	-28	-8	6.73
Hippocampus	L	16	-30	-8	-18	5.99

L = left; R = right; LB, basolateral nucleus; SF, superficial nucleus; PAG, periaqueductal gray. Results of healthy controls are significant at $P_{FWE} < .05$, $k = 4$. Results of patients with LMTLE, RMTLE, and extra-MTLE are significant at $P < .0001$, uncorrected, $k = 4$. [†]Regions included in the cluster immediately above.

Table 4. Region of interest results in bilateral amygdala, bilateral PAG, and right AI.

Region of interest	L/R	MNI coordinates			t-score	P*
		x	y	z		
<i>Healthy controls > LMTLE</i>						
Amygdala (LB)	L	-34	-8	-22	4.74	0.000
Amygdala (LB)	R	30	-4	-22	3.90	0.001
Amygdala (SF)	L	-16	-8	-14	3.77	0.002
Amygdala (LB)	R	24	-10	-12	3.20	0.009
PAG	R	9	-30	-6	3.02	0.015
<i>Healthy controls < LMTLE</i>						
—	—	—	—	—	—	P >.05
<i>Healthy controls > RMTLE</i>						
Amygdala (LB)	R	24	-10	-12	5.19	0.000
Amygdala (LB)	R	30	-4	-22	4.47	0.000
PAG	R	9	-30	-6	3.57	0.003
Amygdala (LB)	L	-34	-8	-22	2.76	0.029
PAG	L	-4	-30	-6	2.62	0.041
<i>Healthy controls < RMTLE</i>						
—	—	—	—	—	—	P >.05
<i>Healthy controls > extra-MTLE</i>						
Amygdala (LB)	R	24	-10	-12	3.34	0.006
<i>Healthy controls < extra-MTLE</i>						
—	—	—	—	—	—	P >.05
<i>LMTLE > RMTLE</i>						
Amygdala (LB)	R	24	-10	-12	2.73	0.036
<i>LMTLE < RMTLE</i>						
—	—	—	—	—	—	P >.05
<i>LMTLE > extra-MTLE, LMTLE < extra-MTLE</i>						
—	—	—	—	—	—	P >.05
<i>RMTLE > extra-MTLE, RMTLE < extra-MTLE</i>						
—	—	—	—	—	—	P >.05

L = left; R = right; LB, basolateral nucleus; SF, superficial nucleus; PAG, periaqueductal gray. * P-values were Bonferroni-corrected for the number of ROIs included in the analyses.

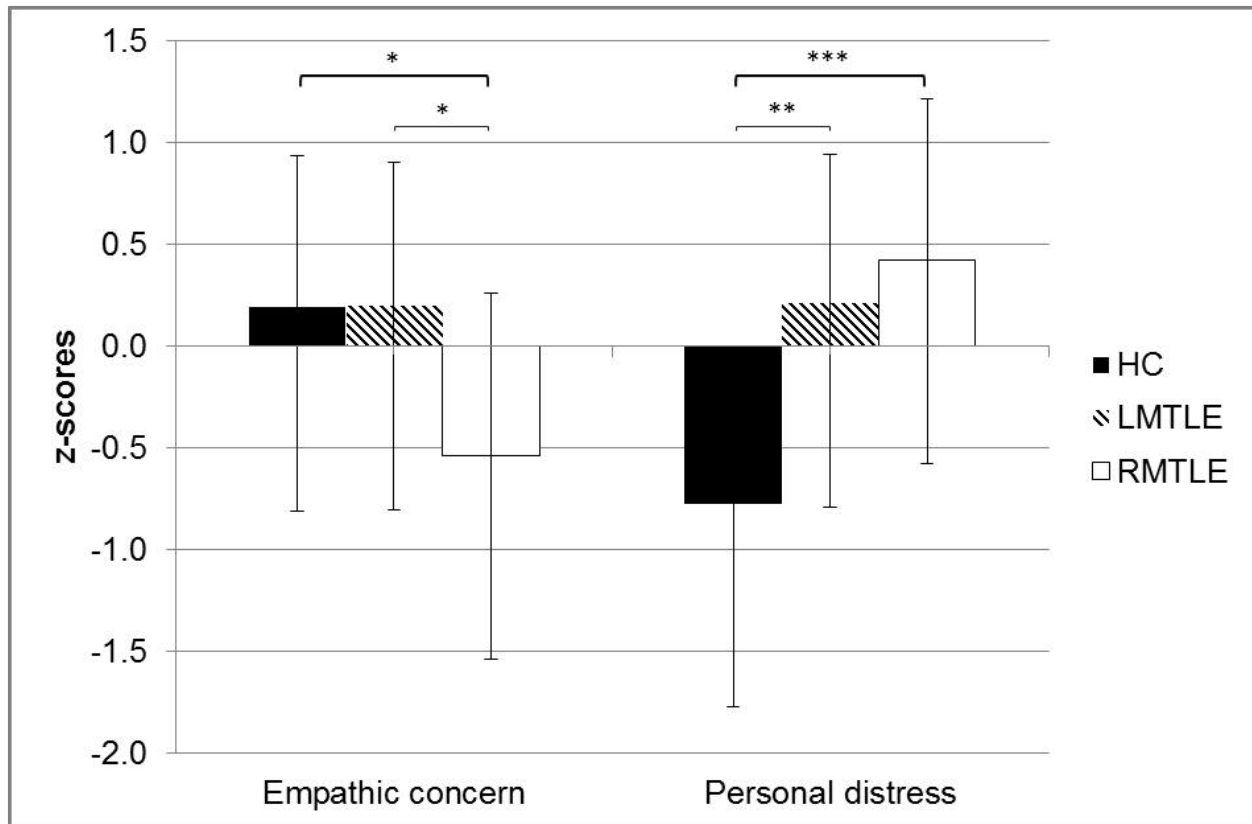


Figure 1. Standardized mean SPF scores, norm-adjusted for age and controlled for depressive symptoms, by diagnostic group (healthy controls (HC), $n = 29$; LMTLE, $n = 9$; RMTLE, $n = 12$; Table 2, p. 60). Empathic concern (EC) scores were lower in RMTLE patients than in healthy controls and LMTLE patients. Both LMTLE and RMTLE groups reported higher levels of personal distress (PD) compared to healthy controls. Significant group differences are denoted by $*P < .05$, $**P < .01$, and $***P < .001$, FDR-corrected for multiple comparisons. Error bars represent SDs.

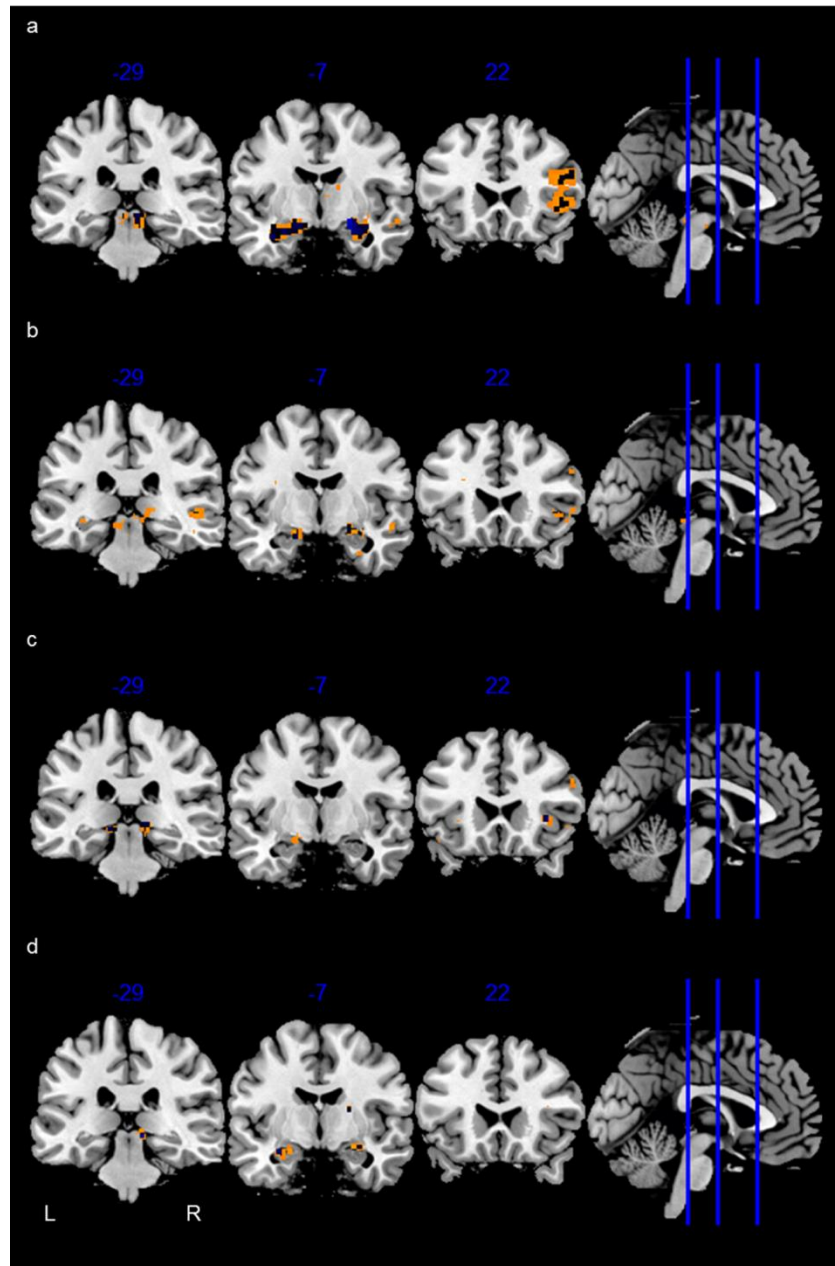


Figure 2. T-score maps (fearful faces > landscapes) showing increased activity in midbrain ($y = -29$), mesial temporal lobe (amygdala, anterior hippocampus; $y = -7$), and anterior insula ($y = 22$) of healthy controls (A), patients with LMTLE (B), RMTLE (C), and extra-MTLE (D). In healthy controls, statistical maps are displayed at $P_{FWE} < .05$, $k = 4$ (blue), and $P < .0001$, uncorrected, $k = 4$ (orange). In LMTLE, RMTLE, and extra-MTLE groups, statistical maps are shown at $P < .0001$, uncorrected, $k = 4$ (blue), and $P < .001$, uncorrected, $k = 4$ (orange). Coordinates refer to MNI space. L = left; R = right.

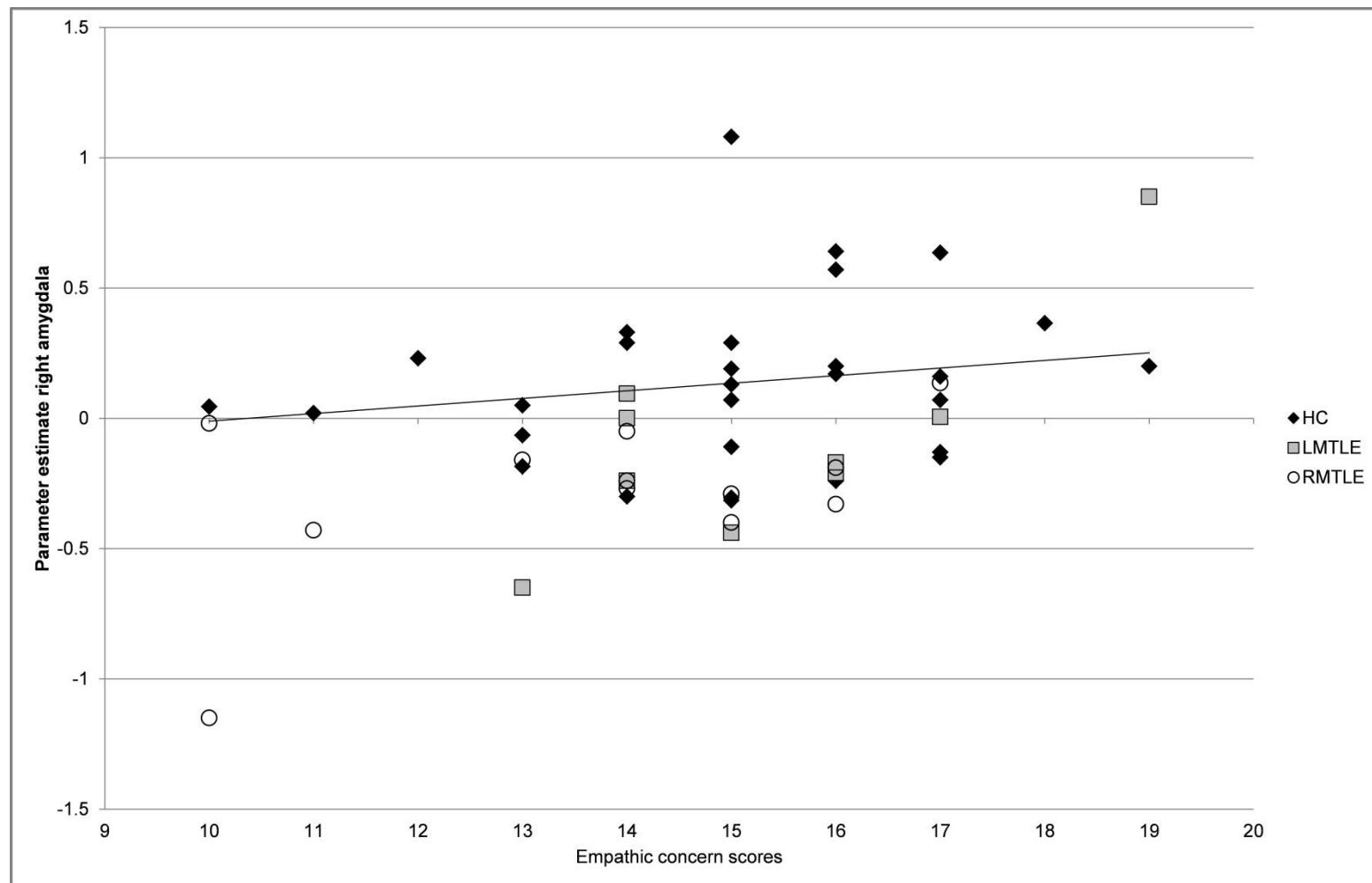


Figure 3. Scatterplot of mean activity in right amygdala versus empathic concern scores across groups (healthy controls (HC), $n = 29$; LMTLE, $n = 9$; RMTLE, $n = 12$; Table 2, p. 60) when controlling for age and depressive symptoms. Higher activity in right amygdala (24, -10, -12) was associated with higher self-reported empathic concern ($r = 0.39$, $P < .05$, Bonferroni-corrected for the number of ROIs). The line represents the linear best fit.

References

- Adolphs, R., Damasio, H., Tranel, D., & Damasio, A. R. (1996). Cortical systems for the recognition of emotion in facial expressions. *The Journal of Neuroscience*, 16, 7678-7687.
- Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, 372, 669-672.
- Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., . . . Damasio, A. R. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, 37, 1111-1117.
- Ansakorpi, H., Korpelainen, J. T., Huikuri, H. V., Tolonen, U., Myllyla, V. V., & Isojarvi, J. I. (2002). Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry*, 72, 26-30.
- Batut, A. C., Gounot, D., Namer, I. J., Hirsch, E., Kehrli, P., & Metz-Lutz, M. N. (2006). Neural responses associated with positive and negative emotion processing in patients with left versus right temporal lobe epilepsy. *Epilepsy & Behavior*, 9, 415-423.
- Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Annals of Statistics*, 29, 1165-1188.
- Benuzzi, F., Meletti, S., Zamboni, G., Calandra-Buonaura, G., Serafini, M., Lui, F., . . . Nichelli, P. (2004). Impaired fear processing in right mesial temporal sclerosis: a fMRI study. *Brain Research Bulletin*, 63, 269-281.
- Bonelli, S. B., Powell, R., Yogarajah, M., Thompson, P. J., Symms, M. R., Koepp, M. J., & Duncan, J. S. (2009). Preoperative amygdala fMRI in temporal lobe epilepsy. *Epilepsia*, 50, 217-227.
- Bonora, A., Benuzzi, F., Monti, G., Mirandola, L., Pugnaghi, M., Nichelli, P., & Meletti, S. (2011). Recognition of emotions from faces and voices in medial temporal lobe epilepsy. *Epilepsy & Behavior*, 20, 648-654.
- Borod, J. C., Cicero, B. A., Obler, L. K., Welkowitz, J., Erhan, H. M., Santschi, C., . . . Whalen, J. R. (1998). Right hemisphere emotional perception: evidence across multiple channels. *Neuropsychology*, 12, 446-458.

- Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., . . . Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*, 17, 875-887.
- Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). Region of interest analysis using the MarsBar toolbox for SPM 99. *Neuroimage*, 16, p. 497.
- Broicher, S. D., Frings, L., Huppertz, H. J., Grunwald, T., Kurthen, M., Kramer, G., & Jokeit, H. (2012). Alterations in functional connectivity of the amygdala in unilateral mesial temporal lobe epilepsy. *Journal of Neurology*, 259, 2546-2554.
- Broicher, S. D., Kuchukhidze, G., Grunwald, T., Krämer, G., Kurthen, M., & Jokeit, H. (2012). “Tell me how do I feel”—Emotion recognition and theory of mind in symptomatic mesial temporal lobe epilepsy. *Neuropsychologia*, 50, 118-128.
- Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience & Biobehavioral Reviews*, 26, 321-352.
- Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*, 3, 655-666.
- Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology*, 13, 500-505.
- Craig, A. D. (2005). Forebrain emotional asymmetry: a neuroanatomical basis? *Trends in Cognitive Sciences*, 9, 566-571.
- Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, 10, 59-70.
- Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, 7, 189-195.
- Davis, M. H. (1983). Measuring individual differences in empathy: evidence for a multidimensional approach. *Journal of Personality and Social Psychology*, 44, 113-126.
- Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, 15, 353-375.
- de Gelder, B., Snyder, J., Greve, D., Gerard, G., & Hadjikhani, N. (2004). Fear fosters flight: a mechanism for fear contagion when perceiving emotion expressed by a whole body.

- Proceedings of the National Academy of Sciences of the United States of America*, 101, 16701-16706.
- de Greck, M., Wang, G., Yang, X., Wang, X., Northoff, G., & Han, S. (2012). Neural substrates underlying intentional empathy. *Social Cognitive and Affective Neuroscience*, 7, 135-144.
- Decety, J., & Lamm, C. (2006). Human empathy through the lens of social neuroscience. *The Scientific World Journal*, 6, 1146-1163.
- Druschky, A., Hilz, M. J., Hopp, P., Platsch, G., Radespiel-Troger, M., Druschky, K., . . . Neundorfer, B. (2001). Interictal cardiac autonomic dysfunction in temporal lobe epilepsy demonstrated by [(123)I]metaiodobenzylguanidine-SPECT. *Brain*, 124, 2372-2382.
- Eisenberg, N., & Strayer, J. (1990). *Empathy and its development*. Cambridge, MA: Cambridge University Press.
- Fan, Y., Duncan, N. W., de Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neuroscience & Biobehavioral Reviews*, 35, 903-911.
- Friston, K. J., Ashburner, J. T., Kiebel, S. J., Nichols, T. E., & Penny, W. D. (2007). *Statistical parametric mapping: the analysis of functional brain images*. London: Academic Press.
- Gallese, V. (2001). The 'shared manifold' hypothesis. From mirror neurons to empathy. *Journal of Consciousness Studies*, 8, 5-7.
- Giovagnoli, A. R., Franceschetti, S., Reati, F., Parente, A., Maccagnano, C., Villani, F., & Spreafico, R. (2011). Theory of mind in frontal and temporal lobe epilepsy: cognitive and neural aspects. *Epilepsia*, 52, 1995-2002.
- Gu, X., Gao, Z., Wang, X., Liu, X., Knight, R. T., Hof, P. R., & Fan, J. (2012). Anterior insular cortex is necessary for empathetic pain perception. *Brain*, 135, 2726-2735.
- Hillis, A. E. (2013). Inability to empathize: brain lesions that disrupt sharing and understanding another's emotions. *Brain*, 137, 981-997.
- Hlobil, U., Rathore, C., Alexander, A., Sarma, S., & Radhakrishnan, K. (2008). Impaired facial emotion recognition in patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS): side and age at onset matters. *Epilepsy Research*, 80, 150-157.

- Jokeit, H., Okujava, M., & Woermann, F. G. (2001). Carbamazepine reduces memory induced activation of mesial temporal lobe structures: a pharmacological fMRI-study. *BMC Neurology*, 1, 6.
- Kanner, A. M., Schachter, S. C., Barry, J. J., Hersdorffer, D. C., Mula, M., Trimble, M., . . . Gilliam, F. (2012). Depression and epilepsy: epidemiologic and neurobiologic perspectives that may explain their high comorbid occurrence. *Epilepsy & Behavior*, 24, 156-168.
- Kida, I., Smith, A. J., Blumenfeld, H., Behar, K. L., & Hyder, F. (2006). Lamotrigine suppresses neurophysiological responses to somatosensory stimulation in the rodent. *Neuroimage*, 29, 216-224.
- Labudda, K., Mertens, M., Steinkroeger, C., Bien, C. G., & Woermann, F. G. (2013). Lesion side matters - An fMRI study on the association between neural correlates of watching dynamic fearful faces and their evaluation in patients with temporal lobe epilepsy. *Epilepsy & Behavior*, 31, 321-328.
- Lamm, C., Batson, C. D., & Decety, J. (2007). The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience*, 19, 42-58.
- Lamm, C., Decety, J., & Singer, T. (2011). Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage*, 54, 2492-2502.
- LeDoux, J. E. (1996). *The emotional brain*. New York: Simon and Schuster.
- Leigh, R., Oishi, K., Hsu, J., Lindquist, M., Gottesman, R. F., Jarso, S., . . . Hillis, A. E. (2013). Acute lesions that impair affective empathy. *Brain*, 136, 2539-2549.
- Mather, M. (2012). The emotion paradox in the aging brain. *Annals of the New York Academy of Sciences*, 1251, 33-49.
- McClelland, S., 3rd, Garcia, R. E., Peraza, D. M., Shih, T. T., Hirsch, L. J., Hirsch, J., & Goodman, R. R. (2006). Facial emotion recognition after curative nondominant temporal lobectomy in patients with mesial temporal sclerosis. *Epilepsia*, 47, 1337-1342.
- Meletti, S., Benuzzi, F., Cantalupo, G., Rubboli, G., Tassinari, C. A., & Nichelli, P. (2009). Facial emotion recognition impairment in chronic temporal lobe epilepsy. *Epilepsia*, 50, 1547-1559.

- Meletti, S., Benuzzi, F., Rubboli, G., Cantalupo, G., Stanzani Maserati, M., Nichelli, P., & Tassinari, C. A. (2003). Impaired facial emotion recognition in early-onset right mesial temporal lobe epilepsy. *Neurology*, 60, 426-431.
- Mobbs, D., Marchant, J. L., Hassabis, D., Seymour, B., Tan, G., Gray, M., . . . Frith, C. D. (2009). From threat to fear: the neural organization of defensive fear systems in humans. *The Journal of Neuroscience*, 29, 12236-12243.
- Mobbs, D., Yu, R., Rowe, J. B., Eich, H., FeldmanHall, O., & Dalgleish, T. (2010). Neural activity associated with monitoring the oscillating threat value of a tarantula. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 20582-20586.
- Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., & Dolan, R. J. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature*, 383, 812-815.
- Paulus, C. (2009). Der Saarbrücker Persönlichkeitsfragebogen SPF (IRI) zur Messung von Empathie: Psychometrische Evaluation der deutschen Version des Interpersonal Reactivity Index. Available from: <http://psydok.sulb.uni-saarland.de/volltexte/2009/2363/>.
- Preston, S. D., & De Waal, F. (2002). Empathy: its ultimate and proximate bases. *Behavioral Brain Sciences*, 25, 1-20.
- Price, J. L. (1999). Prefrontal cortical networks related to visceral function and mood. *Annals of the New York Academy of Sciences*, 877, 383-396.
- Rankin, K. P., Gorno-Tempini, M. L., Allison, S. C., Stanley, C. M., Glenn, S., Weiner, M. W., & Miller, B. L. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain*, 129, 2945-2956.
- Saarela, M. V., Hlushchuk, Y., Williams, A. C. d. C., Schürmann, M., Kalso, E., & Hari, R. (2007). The compassionate brain: humans detect intensity of pain from another's face. *Cerebral Cortex*, 17, 230-237.
- Schacher, M., Haemmerle, B., Woermann, F. G., Okujava, M., Huber, D., Grunwald, T., . . . Jokeit, H. (2006). Amygdala fMRI lateralizes temporal lobe epilepsy. *Neurology*, 66, 81-87.
- Schacher, M., Winkler, R., Grunwald, T., Kraemer, G., Kurthen, M., Reed, V., & Jokeit, H. (2006). Mesial temporal lobe epilepsy impairs advanced social cognition. *Epilepsia*, 47, 2141-2146.

- Sedda, A., Rivolta, D., Scarpa, P., Burt, M., Frigerio, E., Zanardi, G., . . . Bottini, G. (2013). Ambiguous emotion recognition in temporal lobe epilepsy: the role of expression intensity. *Cognitive, Affective, & Behavioral Neuroscience*, 13, 452-463.
- Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., . . . Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience*, 27, 2349-2356.
- Shamay-Tsoory, S. G. (2011). The neural bases for empathy. *The Neuroscientist*, 17, 18-24.
- Shamay-Tsoory, S. G., Lester, H., Chisin, R., Israel, O., Bar-Shalom, R., Peretz, A., . . . Aharon-Peretz, J. (2005). The neural correlates of understanding the other's distress: a positron emission tomography investigation of accurate empathy. *Neuroimage*, 27, 468-472.
- Sherman, E., Griffiths, S. Y., Akdag, S., Connolly, M. B., Slick, D. J., & Wiebe, S. (2008). Sociodemographic correlates of health-related quality of life in pediatric epilepsy. *Epilepsy & Behavior*, 12, 96-101.
- Singer, T. (2006). The neuronal basis and ontogeny of empathy and mind reading: review of literature and implications for future research. *Neuroscience & Biobehavioral Reviews*, 30, 855-863.
- Singer, T., Critchley, H. D., & Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences*, 13, 334-340.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, 303, 1157-1162.
- St Jacques, P. L., Bessette-Symons, B., & Cabeza, R. (2009). Functional neuroimaging studies of aging and emotion: fronto-amygdalar differences during emotional perception and episodic memory. *Journal of the International Neuropsychological Society*, 15, 819-825.
- Sturm, V. E., Yokoyama, J. S., Seeley, W. W., Kramer, J. H., Miller, B. L., & Rankin, K. P. (2013). Heightened emotional contagion in mild cognitive impairment and Alzheimer's disease is associated with temporal lobe degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, 110, 9944-9949.
- Tomasi, D., & Volkow, N. D. (2011). Association between functional connectivity hubs and brain networks. *Cerebral Cortex*, 21, 2003-2013.

- Waxman, S. G., & Geschwind, N. (1975). The interictal behavior syndrome of temporal lobe epilepsy. *Archives of General Psychiatry*, 32, 1580-1586.
- Wicker, B., Keysers, C., Plailly, J., Royet, J.-P., Gallese, V., & Rizzolatti, G. (2003). Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. *Neuron*, 40, 655-664.
- Windischberger, C., Lanzenberger, R., Holik, A., Spindelegger, C., Stein, P., Moser, U., . . . Kasper, S. (2010). Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmacofMRI: a randomized cross-over study. *Neuroimage*, 49, 1161-1170.
- Woermann, F. G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., . . . Ebner, A. (2003). Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology*, 61, 699-701.

Supplementary Table 1. Clinical characteristics of patients with extra-MTLE.

Patient	Classification of epilepsy	Etiology	Localization of lesion	Side of lesion
1	Non-lesional	Unknown	Temporo-lateral [†]	L/R [†]
2	Non-lesional	Unknown	Occipital, baso-lateral [†]	L [†]
3	Non-lesional	Unknown	Temporo-lateral [†]	L [†]
4	Non-lesional	Unknown	Temporo-lateral [†]	L [†]
5	Non-lesional	Unknown	Frontal [†]	R [†]
6	Lesional	Ischemia	Parieto-occipital	L
7	Lesional	Cortical dysplasia	Fronto-polar	L
8	Lesional	Cortical dysplasia	Fronto-lateral	R
9	Lesional	Ganglioglioma	Temporo-polar	R
10	Lesional	Ganglioglioma	Temporo-occipital, basal	R
11	Lesional	Cortical dysplasia	Fronto-lateral	L
12	Lesional	Cavernoma	Temporo-lateral	L
13	Lesional	Cortical dysplasia	Temporo-occipital, postero-basal	R
14	Lesional	Ganglioglioma	Temporo-basal	L
15	Lesional	Cortical dysplasia	Fronto-basal	L
16	Lesional	Astrocytoma	Temporo-lateral	R

L = left, R = right [†] Localization and side of seizure onset is indicated for patients with non-lesional extra-MTLE.

Supplementary Table 2. Daily doses (mg) of antiepileptic and antidepressant medication used in each patient.

Group Patient Statistics	AEDs ^a						Antidepressants				
	LTG	LEV	CBZ	OXC	VPA	Other	MIR	VEN	SER	FLX	ESC
LMTLE											
1	500	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	1500	LCM	—	—	—	—	—
3	—	1000	—	600	1000	—	—	—	—	—	—
4	—	3000	1600	—	—	—	—	—	—	—	—
5	75	2500	—	—	—	—	—	—	50	—	—
6	—	3500	—	1800	—	CLB	—	—	—	—	—
7	500	—	1000	—	—	—	—	—	—	—	—
8	—	2000	—	—	2000	—	—	75	—	—	—
9	425	3500	—	—	—	ZNS	—	—	—	—	—
10	—	—	800	—	—	—	—	—	—	—	—
11	—	3000	—	—	—	—	—	—	50	—	—
12	100	—	—	—	—	CLB	—	—	—	—	—
13	—	1000	—	—	—	—	—	—	—	—	—
14	350	—	—	—	—	CLB	—	—	—	—	—
15	—	3000	—	—	—	PHT	—	—	—	60	—
16	—	2500	—	—	—	CLB, PB	15	—	—	—	—
% n ^b	37.5	62.53	18.8	12.5	18.8	—	6.3	6.3	12.5	6.3	0.0
RMTLE											
1	350	—	—	—	1000	—	—	—	—	—	—
2	400	—	—	—	—	—	—	—	—	—	—
3	400	—	—	—	—	—	—	—	—	—	—
4	—	—	—	—	—	PHT	—	—	—	—	—
5	—	—	800	—	—	TPM	—	—	50	—	—
6	400	—	1600	—	—	—	—	—	—	—	—
7	400	—	—	—	—	—	—	—	—	—	—

Research publications

Group Patient Statistics	AEDs ^a		Antidepressants								
	LTG	LEV	CBZ	OXC	VPA	Other	MIR	VEN	SER	FLX	ESC
8	500	3000	—	—	—	—	—	—	—	—	—
9	600	—	—	—	—	—	—	—	—	—	—
10	250	—	—	—	—	—	—	—	50	—	—
11	—	2000	1200	—	—	—	—	—	—	—	—
12	175	—	—	—	—	—	—	—	—	—	—
13	—	—	—	1500	—	—	—	—	—	—	—
14	—	3000	—	—	—	ZNS	—	—	—	—	—
15	450	1000	—	—	—	CLB	—	—	—	—	—
16	—	3500	—	—	—	—	—	—	—	—	—
17	425	—	—	—	—	—	30	—	—	—	20
18	400	—	—	—	—	—	—	—	—	—	—
% <i>n</i> ^b	66.7	27.8	16.7	5.6	5.6	—	5.6	0.0	11.1	0.0	5.6
extra-MTLE											
1	450	—	—	—	—	ZNS	30	—	—	—	—
2	—	—	—	900	—	—	—	—	—	—	—
3	500	3000	—	2100	—	—	—	—	—	—	—
4	—	3500	—	—	—	—	—	—	—	—	—
5	—	—	1200	—	—	—	—	—	—	—	—
6	—	2500	—	—	—	—	—	—	—	—	—
7	—	3000	—	—	—	—	—	—	—	—	—
8	500	1500	—	—	—	CZP	—	—	100	—	—
9	—	2000	1200	—	—	—	—	—	—	—	—
10	—	3000	—	1350	—	—	—	—	—	—	—
11	200	3500	—	—	—	—	—	—	—	—	—
12	250	2000	—	—	—	—	—	—	—	—	—
13	300	4000	—	1800	—	—	—	—	—	—	—
14	500	3000	—	—	—	—	—	—	—	—	—

Research publications

Group Patient Statistics	AEDs ^a		Antidepressants								
	LTG	LEV	CBZ	OXC	VPA	Other	MIR	VEN	SER	FLX	ESC
15	550	—	—	—	—	—	—	—	—	—	—
16	400	1500	—	—	—	CLB	—	—	75	—	—
% <i>n</i> ^b	56.2	75.0	12.5	25.0	0.0	—	6.3	0.0	12.5	0.0	0.0

^a AEDs, antiepileptic drugs; LTG, Lamotrigine; LEV, Levetiracetam; CBZ, Carbamazepine; OXC, Oxcarbazepine; VPA, Valproic acid; LCM, Lacosamide; CLB, Clobazam; ZNS, Zonisamide; PHT, Phenytoin; PB, Phenobarbital; TPM, Topiramate; CZP, Clonazepam; MIR, Mirtazapine; VEN, Venlafaxine; SER, Sertraline; FLX, Fluoxetine; ESC, Escitalopram. ^b Percentage of patients per group (LMTLE, RMTLE, extra-MTLE) treated with each antiepileptic and antidepressant substance. Chi-square statistics demonstrated that the three epilepsy groups differed only on the number of patients treated with levetiracetam ($\chi^2(2) = 8.3, P < .05$), with the highest percentage found in the extra-MTLE group.

3.3 Right fronto-limbic atrophy is associated with reduced empathy in refractory unilateral mesial temporal lobe epilepsy

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Abstract

Refractory mesial temporal lobe epilepsy (MTLE) is the most frequent focal epilepsy and is often accompanied by deficits in social cognition including emotion recognition, theory of mind, and empathy. Consistent with the neuronal networks that are crucial for normal social-cognitive processing, these impairments have been associated with functional changes in fronto-temporal regions. However, although atrophy in unilateral MTLE also affects regions of the temporal and frontal lobes that underlie social cognition, little is known about the structural correlates of social-cognitive deficits in refractory MTLE. In the present study, a psychometrically validated empathy questionnaire was combined with whole-brain voxel-based morphometry (VBM) to investigate the relationship between self-reported affective and cognitive empathy and gray matter volume in 55 subjects (13 patients with right MTLE, 9 patients with left MTLE, and 33 healthy controls). Consistent with the brain regions underlying social cognition, our results show that lower affective and cognitive empathy was associated with smaller volume in predominantly right fronto-limbic regions, including the right hippocampus, parahippocampal gyrus, thalamus, fusiform gyrus, inferior temporal gyrus, dorsomedial and dorsolateral prefrontal cortices, and in the bilateral midbrain. The only region that was associated with both affective and cognitive empathy was the right mesial temporal lobe. These findings indicate that patients with right MTLE are at increased risk for reduced empathy towards others' internal states and they shed new light on the structural correlates of impaired social cognition frequently accompanying refractory MTLE. In line with previous evidence from patients with neurodegenerative disease and stroke, the present study suggests that empathy depends upon the integrity of right fronto-limbic and brainstem regions and highlights the importance of the right mesial temporal lobe and midbrain structures for human empathy.

Key words: mesial temporal lobe epilepsy, empathy, voxel-based morphometry

Introduction

Empathy, the ability to share the feelings of others, is a prerequisite for successful prosocial interaction and stable social relationships (Eisenberg & Strayer, 1990; Preston & De Waal, 2002). Although a consensus on its precise definition is yet to be reached, there is broad agreement that empathy is a multidimensional construct that encompasses both affective and cognitive processes with different neurodevelopmental trajectories and neural underpinnings (Eisenberg & Strayer, 1990; Preston & De Waal, 2002; Singer et al., 2004; Decety & Lamm, 2006; Singer, 2006).

Based on developmental, neurobehavioral, and neuroscientific findings, Decety and colleagues (e.g., Decety & Jackson, 2004; Decety, 2005; Decety & Meyer, 2008) have proposed a comprehensive and integrative framework showing that empathy derives from a number of distinct and interacting bottom-up and top-down processes that are mediated by various cortical and subcortical brain regions. Accordingly, the first step towards the feeling of empathy involves the bottom-up process of affective sharing that relies predominantly on limbic structures such as the amygdala and the hippocampus (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Decety & Chaminade, 2003; Völlm et al., 2006). Secondly, empathy involves the recognition that the source of a shared emotion is located outside oneself which requires emotion awareness and emotion understanding that draw mainly on frontal regions including the anterior insula, the medial and the dorsolateral prefrontal cortex (mPFC, dlPFC; Gallagher & Frith, 2003; Craig, 2009). Finally, an essential aspect of empathy is to maintain a clear separation between self and other which is mediated by fronto-parietal circuits involving the orbitofrontal cortex, the mPFC, the dlPFC, and the temporo-parietal junction (Decety & Sommerville, 2003; Saxe & Wexler, 2005; Decety & Lamm, 2007).

Consistent with the multifaceted nature of empathy, which is mediated by a distributed network of predominantly fronto-temporal and also parietal brain regions, many neuropsychiatric and neurological disorders including schizophrenia, Asperger's syndrome, traumatic brain injury, stroke, and neurodegenerative disease have been shown to be associated with altered empathic behavior (Perry et al., 2001; Baron-Cohen & Wheelwright, 2004; Rankin et al., 2006; Wood & Williams, 2008; Derntl et al., 2009; Leigh et al., 2013; Hillis, 2014). The previous studies that have quantified brain-empathy relationships in patients with

relatively circumscribed brain lesions overall suggest that the medial and lateral parts of the prefrontal and temporal cortices and the inferior parietal lobe of the right hemisphere are critical for normal empathic behavior (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Rankin, Kramer, & Miller, 2005; Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz, 2005; Rankin et al., 2006; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009; Leigh et al., 2013; Hillis, 2014).

Intractable unilateral mesial temporal lobe epilepsy (MTLE) is a chronic neurological disorder that is associated with structural damage to the epileptogenic mesial temporal lobe (Keller & Roberts, 2008). Voxel-based morphometry (VBM) studies and post-mortem studies have clearly shown that gray and white matter loss in MTLE is not restricted to the epileptogenic mesial temporal lobes but also affects regions of the lateral temporal, frontal, and parietal cortices that overlap extensively with structures mediating the affective and cognitive components of empathy (Keller & Roberts, 2008; Bonilha et al., 2010). Consequently, VBM is a valid imaging technique to detect both cortical and subcortical morphological changes in this patient population. Previous research has also demonstrated that VBM provides a suitable method to study the relationship between mesial- and extra-temporal atrophy and (social-) cognitive impairments frequently associated with MTLE (Focke, Thompson, & Duncan, 2008; Keller, Baker, Downes, & Roberts, 2009; Cohn, St-Laurent, Barnett, & McAndrews, 2014).

However, despite the evidence that MTLE is associated with brain atrophy in temporal, frontal, and parietal regions that are critical for the affective and cognitive aspects of empathy, previous research has neglected to investigate the structural correlates of empathy in unilateral MTLE. Therefore, in the present study, we combined a psychometrically validated empathy questionnaire that has previously been applied to study brain-empathy relationships in both healthy and neurological populations with whole-brain VBM analyses in patients with unilateral MTLE and in matched healthy controls. The aims of the present study were twofold. Firstly, we intended to investigate whether self-reported affective and cognitive aspects of empathy are differentially affected by left and right MTLE (LMTLE, RMTLE). Secondly, we aimed to study whether regional differences in gray matter volume of MTLE patients are related to their empathic behavior. Given that right and left MTLE are associated with strongly asymmetric and opposite patterns of mesial temporal atrophy, the two groups provide suitable lesion models to

investigate the relative significance of the right and left mesial temporal lobe involvement for normal empathic behavior. Based on preceding human lesion studies showing that right fronto-temporal regions in particular are critical for human empathy, our primary hypothesis was that right hemisphere atrophy in temporal and extra-temporal regions would be associated with reduced empathy in unilateral MTLE.

Methods

Participants

A total of 55 participants (33 healthy controls, 9 patients with LMTLE, 13 with RMTLE) were included in the present study. Sixty consecutive patients with medically refractory unilateral MTLE, undergoing comprehensive presurgical evaluation at the Swiss Epilepsy Center Zurich, were recruited between 2007 and 2014. A total of 22 patients fulfilled the following inclusion criteria and were finally included in the analyses: unilateral hippocampal sclerosis (HS) demonstrated by axial and coronal T1- and T2-weighted high-resolution MR images; unilateral seizure onset of temporal origin shown by continuous interictal and ictal video-EEG monitoring with scalp and intracranial (2%) electrodes; concordance between the side of HS and the side of seizure onset; no bilateral HS; no additional brain pathologies. In addition, only patients with normal intelligence (IQ score greater than 75) and intact reading comprehension were recruited to exclude the possibility that cognitive dysfunctions could interfere with responses on the empathy questionnaire. Due to the relatively high prevalence of affective disorders in epilepsy patients (for a review see Kanner et al., 2012), mild to moderate depressive symptoms identified by psychiatric interviews were not exclusion criteria. At the time of MRI scanning, all patients were treated with antiepileptic drugs (AEDs) either as mono- (LMTLE = 44%; RMTLE = 62%) or polytherapy (LMTLE = 56%; RMTLE = 38%). Based on clinical histories and structural MRI, all healthy controls were free of current or previous neurological or psychiatric disorders, alcohol or substance abuse, and chemotherapy. Except for education and the presence of depressive symptoms, the diagnostic groups did not differ significantly in demographic and clinical variables (Table 1, p. 92). Supplementary Table 1 (p. 103) shows each patient's possible etiology of hippocampal sclerosis and seizure frequency at the time of MRI scanning. All patients and controls provided written informed consent. The study was approved by the local ethics

committee and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Behavioral measures

Empathy questionnaire

The subjects completed the Saarbruecker Personality Questionnaire (SPF; Paulus, 2009), an adapted and psychometrically validated German version of the Interpersonal Reactivity Index (IRI; Davis, 1983), within 12 months of the structural MRI scanning. According to both cross-sectional and longitudinal studies, cortical and subcortical gray matter volumes in patients with refractory temporal lobe epilepsy remain stable within one year of disease progression (Fuerst, Shah, Shah, & Watson, 2003; Bernhardt et al., 2009). The 16-item SPF is a self-report questionnaire composed of four subscales that evaluate both affective and cognitive aspects of empathy: Empathic Concern (EC: the other-oriented feelings elicited by another's emotional state) and Personal Distress (PD: self-oriented feelings of anxiety and unease in tense interpersonal settings) were designed to measure the affective aspects of empathy. As the psychometric validity of the PD subscale is limited (Paulus, 2009), only the better-validated EC scale was used in this study to assess the emotional elements of empathy. The second pair of SPF subscales was designed to measure the cognitive aspects of empathy: Perspective Taking (PT: the spontaneous adoption of another's cognitive perspective) and Fantasy (FS: the tendency to project oneself into feelings and actions of fictional characters). However, as the FS subscale correlates more with measures of emotionality than cognitive empathy, only the PT subscale was used in the present study to assess the cognitive aspects of empathy. Higher EC and PT scores represent a more developed capacity for empathizing, with scores ranging from 4 to 20 for each subscale.

Analyses

To account for potential age-related effects on self-reported empathy within the three diagnostic groups, each subject's SPF raw scores were transformed into age-adjusted norm values (<http://bildungswissenschaften.uni-saarland.de>). Because mood may have influenced the subjects' self-reports, we included the presence of depressive symptoms as a covariate in the

following analyses. However, because all participants had either attended regular schooling (healthy controls) or had an IQ score greater than 75 (patient groups), we did not adjust for education. Shapiro-Wilk tests of normality indicated that the EC and PT scores were normally distributed within each diagnostic group ($P > .10$). Separate one-way (group: healthy controls, LMTLE, RMTLE) analyses of covariance (controlling for depressive symptoms) were conducted on both EC and PT subscales. Significant main effects were analyzed post hoc using false discovery rate (FDR) correction for multiple comparisons (Benjamini & Yekutieli, 2001).

Neuroimaging

Structural MRI

All structural images were acquired on the same 3.0-T scanner (Philips Medical Systems, Best, The Netherlands), equipped with a 32-channel head coil, using a T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (176 sagittal slices, 1-mm thick, skip = 0 mm; repetition time = 8.1 ms; echo time = 3.7 ms; flip angle = 8°; field of view = 240 x 240 mm²; voxel size = 1 mm³; matrix size = 256 x 256).

Voxel-based morphometry

Preprocessing

Structural T1-weighted images were preprocessed using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) and SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8). The images were visually inspected for artifacts, bias-corrected, and tissue classified (gray matter, white matter, cerebrospinal fluid segments). This was followed by spatial normalization of the segmented images to MNI space (Ashburner & Friston, 2005), using affine and nonlinear transformations with the help of the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) method, as implemented in the toolbox (Ashburner & Friston, 2005; Ashburner, 2007). The DARTEL method was also used to create a customized template from all study participants ($n = 55$). In all preprocessing steps, default parameters of the VBM8 toolbox were used, with the exception of using the light clean-up procedure in the morphological filtering step. The spatially normalized, segmented, and modulated gray matter images were smoothed with an 8-mm FWHM isotropic Gaussian kernel.

Analyses

To confirm the strongly asymmetric and opposite patterns of atrophy within the mesial temporal lobes of the RMTLE and LMTLE groups, differences in gray matter volumes between each pair of group were assessed using two-sample *t*-tests, with age, education, total intracranial volume (to account for individual differences in head size), and depressive symptoms included in the analyses. A statistical threshold of $P < .0001$, uncorrected, $k = 10$ was applied to all between-group contrasts. Next, covariates-only statistical models were conducted to correlate the whole-brain gray matter maps of all study participants ($n = 55$) separately with the EC and PT scores. The reasons for the inclusion of all diagnostic groups (healthy controls, RMTLE, LMTLE) into the same regression analyses were to obtain a larger study sample and to have greater variance at both the brain and behavioral level, which increased the study's statistical power to detect brain-behavior relationships (Rankin et al., 2009; Sollberger et al., 2009). Age, education, total intracranial volume, and depressive symptoms were included in the whole-brain regression analyses. We adjusted for the presence of depressive symptoms because of previous VBM studies demonstrating that gray matter atrophy is more pronounced in MTLE patients with than without comorbid depression (Shamim, Hasler, Liew, Sato, & Theodore, 2009; Salgado, Yasuda, & Cendes, 2010). The statistical threshold was set at $P < .001$, uncorrected, $k = 20$. Images were overlaid with MRICron (<http://www.mccauslandcenter.sc.edu/CRNL/>) on the MNI standard brain.

Results

Demographic and clinical data

Demographic and clinical data are presented in Table 1 (p. 92). Significant group differences were found in education and the presence of depressive symptoms. The LMTLE and RMTLE groups did not differ with respect to age at epilepsy onset, duration of epilepsy, and the daily number of antiepileptic drugs ($P > .05$).

Empathy questionnaire

The main effect of group was found on both the empathic concern [EC; $F(2, 55) = 5.2$; $P < .01$] and perspective taking [PT; $F(2, 55) = 7.03$; $P < .01$] subscales (Figure 1, p. 94). Post-hoc

pairwise comparisons demonstrated that the RMTLE patients reported significantly lower EC than both the healthy controls ($P < .05$, FDR-corrected) and the LMTLE patients ($P < .05$, FDR-corrected). In addition, the PT scores obtained in the RMTLE group were significantly lower compared with the healthy controls ($P < .01$, FDR-corrected). The difference between the RMTLE and LMTLE patients on the PT subscale was not significant ($P > .05$). Figure 1 (p. 94) shows that both the EC and PT scores were widely distributed within each group.

Neuroimaging

Figure 2 (p. 95) illustrates the expected patterns of mesial temporal atrophy in the LMTLE and RMTLE groups. According to two sample t -tests, the patients with LMTLE showed gray matter loss in the left hippocampus/parahippocampal gyrus [$t = 5.19$; Montreal Neurological Institute (MNI) peak, -27, -22, -15; $P < .0001$, uncorrected, $k = 311$] compared to the healthy controls. Consistent with that, the LMTLE group demonstrated lower brain volume in the left hippocampus/parahippocampal gyrus [$t = 6.66$; MNI peak, -26, -22, -17; $P < .0001$, uncorrected, $k = 620$] and the left superior occipital gyrus [$t = 5.00$; MNI peak, -11, -82, 42; $P < .0001$, uncorrected, $k = 31$] than the RMTLE group. By contrast, the RMTLE patients showed atrophy in the right hippocampus/parahippocampal gyrus compared to both the healthy control [$t = 7.37$; MNI peak, 32, -22, -15; $P < .0001$, uncorrected, $k = 986$] and the LMTLE group [$t = 6.01$; MNI peak, 39, -9, -15; $P < .0001$, uncorrected, $k = 351$]. Lower brain volume was further found in the right anterior fusiform gyrus [$t = 5.80$; MNI peak, 15, 5, -44; $P < .0001$, uncorrected, $k = 28$] of the RMTLE patients when compared to the LMTLE patients.

Unbiased whole-brain regression analysis demonstrated that lower EC was associated with smaller gray matter volume in the right ventromedial prefrontal cortex, left dorsomedial prefrontal cortex, right dorsolateral prefrontal cortex, left inferior parietal lobule, and right parahippocampal gyrus ($P < .001$, uncorrected). Table 2 (p. 93) shows the t -scores and the significance levels for each region, and Figure 3 (p. 96) displays the corresponding statistical maps. The same whole brain regression analysis conducted on the PT subscale revealed that lower PT was associated with gray matter atrophy in the right thalamus, bilateral midbrain, right hippocampus, right parahippocampal gyrus, right fusiform gyrus, right inferior temporal gyrus, and right paracentral lobule ($P < .001$, uncorrected).

Discussion

In the present study, VBM was used in patients with medically refractory unilateral MTLE to correlate gray matter volumes with the patients' self-reported ability to empathize with others. Our results show that lower levels of both affective and cognitive empathy were associated with atrophy in predominantly right fronto-limbic regions, including the right mesial temporal lobe (hippocampus and parahippocampal gyrus), right thalamus, right fusiform gyrus, right inferior temporal gyrus, right dorsolateral and bilateral medial prefrontal cortices, and in the bilateral midbrain. Our findings shed new light on the relative impact of focal left and right mesial temporal damage on human empathy and support previous research investigating brain-empathy relationships in patients with circumscribed brain lesions due to neurodegenerative disease and stroke (Shamay-Tsoory et al., 2003; Shamay-Tsoory et al., 2005; Rankin et al., 2006; Shamay-Tsoory et al., 2009; Leigh et al., 2013; Hillis, 2014).

The RMTLE group reported lower EC and PT than the healthy controls, and diminished EC compared to the LMTLE group, which is consistent with previous human lesion studies showing that damage to the right temporal lobe is associated with both impaired affective and cognitive empathy (Perry et al., 2001; Rankin et al., 2005; Rankin et al., 2006; Leigh et al., 2013; Hillis, 2014). Because the presence of depressive symptoms was treated as a nuisance covariate in our statistical analyses, the decreased empathy scores we found in the RMTLE patients cannot be attributed to between-group differences in comorbid depression. Such an asymmetric impact of right and left MTLE on the patients' social-cognitive processing supports previous findings demonstrating that facial emotion recognition, a process involved in empathic experiences (Shamay-Tsoory, 2011), is more impaired in patients with right than left MTLE (Meletti, Benuzzi, Nichelli, & Tassinari, 2003; Meletti et al., 2009).

Our whole-brain VBM analyses demonstrate that self-reported EC and PT in unilateral MTLE is associated with atrophy in predominantly right fronto-limbic regions, including the right ventromedial and dorsolateral prefrontal cortices, left dorsomedial prefrontal cortex, right thalamus, right hippocampus, right parahippocampal gyrus, right fusiform gyrus, right inferior temporal gyrus, and left inferior parietal lobule, and in the bilateral midbrain. This set of brain structures is highly consistent with the regions mediating the bottom-up and top-down processes of empathy that include emotion sharing, emotion understanding, and emotion

regulatory mechanisms required for self-other distinction (Decety, 2011; Fan, Duncan, de Greck, & Northoff, 2011; Lamm, Decety, & Singer, 2011). Atrophy in the right mesial temporal lobe (hippocampus and parahippocampal gyrus) was the only area that was associated with both lower EC and PT. Despite the inclusion of a cohort of MTLE patients with either strongly left-lateralized or right-lateralized mesial temporal damage, the volume in the left mesial temporal lobe was neither related to EC nor to PT, a finding that cannot be attributed to group differences in demographic and clinical variables including sex, age, education, presence of depressive symptoms, age at epilepsy onset, and duration of epilepsy. Considering that extra-temporal atrophy in unilateral MTLE affects both hemispheres relatively symmetrically (Keller & Roberts, 2008), the correlation we found between lower empathy and atrophy in the right thalamus and the right ventromedial and dorsolateral prefrontal cortices further supports the present result of a right hemisphere predominance for normal empathic behavior. The finding that a mainly right fronto-limbic network underlies the ability to empathize in patients with unilateral MTLE confirms previous studies investigating brain-empathy relationships in patients with fronto-temporal damage due to neurodegenerative disease (Perry et al., 2001; Shamay-Tsoory et al., 2003; Shamay-Tsoory et al., 2005; Rankin et al., 2006; Shamay-Tsoory et al., 2009) and stroke (Leigh et al., 2013; Hillis, 2014). Our findings can also be integrated into research on altruism, a more extreme form of prosocial behavior than empathy, demonstrating that an extraordinary tendency for altruistic behaviors is associated with enhanced volume in the right amygdala (Marsh et al., 2014). Based on previous human lesion evidence suggesting that the right inferior parietal lobe is critical for normal empathic behavior (Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004; Hillis, 2014), self-reported empathy was expected to be associated with gray matter volume in the right rather than the left inferior parietal lobe. However, based on functional imaging studies in healthy subjects (Aichhorn et al., 2009; Schurz, Aichhorn, Martin, & Perner, 2013), the left inferior parietal lobe is involved in representing different perspectives in a domain-general fashion, a finding that is consistent with the relationship we found between atrophy in the left inferior parietal lobe and diminished empathy in unilateral MTLE.

The association we found between midbrain atrophy and lower PT confirms recent meta-analyses of task-related fMRI studies demonstrating the region's consistent involvement in

empathy for different bodily and feeling states (Fan et al., 2011; Lamm et al., 2011; Bzdok et al., 2012). This result is also in line with a previous study demonstrating that healthy individuals who reported a higher capacity for cognitive empathy, measured by the IRI as in the present study, showed a stronger intrinsic functional connectivity among different areas implicated in social-cognitive processing, including the brainstem (Cox et al., 2012). Our finding that empathy in unilateral MTLE depends upon the integrity of not only right fronto-limbic brain regions but also on brainstem structures that are part of the autonomic nervous system corroborates early theories of emotion (James, 1884; Lange, 1885) and current models on human awareness (Craig, 2009) and empathy (Singer, Critchley, & Preuschoff, 2009), suggesting that interoceptive information from the body is essential for both firsthand and empathic feeling states. Consistent with this, we have recently demonstrated that unilateral MTLE is associated with decreased empathy-related midbrain activity during the observation of dynamic fearful faces (Toller et al., 2015).

Overall, our results indicate that patients with RMTLE are at increased risk for reduced affective and cognitive empathy towards others' internal states. This finding is in line with our recent study showing that RMTLE was associated with decreased empathy-related responses in the right amygdala and the bilateral midbrain to dynamic fearful faces (Toller et al., 2015). Consequently, we suggest that both structural and functional changes in the right mesial temporal lobe and also in anatomically remote right fronto-limbic and bilateral brainstem regions contribute to diminished empathy in patients with refractory RMTLE. Consistent with the present findings, atrophy in and outside the mesial temporal lobes has recently been linked to social inference deficits in patients with unilateral MTLE (Cohn et al., 2014). However, in contrast to the present findings, Cohn et al. (2014) demonstrated an association between left mesial and lateral temporal atrophy and impaired comprehension of paralinguistic cues displayed during social interactions. The findings that impaired social inference and reduced empathy were related to atrophy in the opposite mesial temporal lobe indicate that depending on the particular social-cognitive process patients with right and left MTLE may have different risks for impaired social cognition.

Although we used a psychometrically validated empathy questionnaire that has previously been used in studies on empathy in both healthy and neurological populations (Shamay-Tsoory

et al., 2004; Shamay-Tsoory et al., 2005; Rankin et al., 2006; Banissy, Kanai, Walsh, & Rees, 2012), we cannot exclude the possibility that the self-ratings of the RMTLE patients in particular may be positively biased due to poor insight associated with their right hemisphere lesion. Such biased responding may also have contributed to the lack of significant differences in cognitive empathy between the two MTLE groups. However, considering this potential source of bias, the finding that the RMTLE group nevertheless reported lower empathy than the LMTLE and healthy control groups is even more remarkable.

From a clinical perspective, our results confirm and extend previous evidence on facial emotion recognition (Meletti, Benuzzi, Nichelli, et al., 2003; Meletti, Benuzzi, Rubboli, et al., 2003; Benuzzi et al., 2004; Hlobil, Rathore, Alexander, Sarma, & Radhakrishnan, 2008; Meletti et al., 2009; Sedda et al., 2013) and social inference abilities (Cohn et al., 2014) indicating that social cognition may be differentially affected in patients with medically refractory left and right MTLE. Further, our results suggest that reduced empathy in MTLE patients cannot merely be attributed to the chronic use of antiepileptic medication and psychosocial factors such as fear of seizures, perceived stigma, and lack of social support but are at least partly caused by structural abnormalities in and outside the mesial temporal lobes. Such insights into the etiopathogenesis of impaired social cognition in MTLE are required for the development and application of therapy programs targeting the social deficits frequently observed in this patient group (Szemere & Jokeit, 2015).

The small sample size of the LMTLE group is a limitation to this study, which is a likely cause for the lack of differences in cognitive empathy we found between the two MTLE groups. In addition, because of the lower number of LMTLE than RMTLE patients, it is possible that we had greater anatomic variability in the right than in the left mesial temporal lobe and, therefore, more statistical power to detect a relationship between empathy and regions of the right than the left mesial temporal lobe.

In summary, this study represents the first investigation on the structural correlates of self-reported empathy in patients with refractory unilateral MTLE. Our results suggest that the extent to which empathy is disrupted in unilateral MTLE depends on the integrity of predominantly right fronto-limbic regions, including the right mesial temporal lobe, and of the brainstem. These neurobehavioral findings indicate that patients with RMTLE are at increased

risk for diminished empathy towards others' internal states, which supports previous neuroimaging evidence on empathy in both healthy and neurological populations. Overall, our study sheds further light on the nature and etiopathogenesis of social-cognitive impairments frequently associated with refractory MTLE and provides new insights into the brain regions that are crucial for normal empathic behavior and successful social functioning in everyday life.

Acknowledgments

The authors acknowledge Dr. Dominik Huber and Thekla Kaisen for technical assistance during fMRI acquisition, and Dr. Victoria Reed for the final edits of the manuscript.

Disclosure statement

The authors have no conflict of interest to disclose.

Funding

This work was supported by the Swiss Epilepsy Foundation.

Table 1. Demographic and clinical information for each diagnostic group.

Demographic and clinical variables	Group			Statistics	<i>P</i>
	Controls (<i>n</i> =33)	LMTLE (<i>n</i> =9)	RMTLE (<i>n</i> =13)		
Sex, % female	51.5	66.7	53.8	$\chi^2(2) = .658$.720
Age, median years (range)	39.1 (22-63)	26.4 (15-53)	46.9 (24-61)	$H(2) = 4.471$.107
Education, median years (range)	16 (12-19)	11 (7-12)	12 (10-15)	$H(2) = 35.507$.000
Language dominance ^a , % atypical	3.3	11.1	15.4	$\chi^2(2) = 2.034$.362
Handedness, % right-handed	90.9	66.7	76.9	$\chi^2(2) = 4.812$.307
Depressive symptoms, % <i>n</i>	0	22.2	38.5	$\chi^2(2) = 13.294$.001
Age at epilepsy onset, mean years (<i>SD</i>)	—	14.2 (9.6)	18.4 (16.4)	$t(20) = -.748$.463
Duration of epilepsy, mean years (<i>SD</i>)	—	16.6 (15.3)	24.9 (13.0)	$t(20) = -1.368$.186
AEDs ^b , <i>n</i> per day (range)	—	2.0 (1-3)	1.0 (1-3)	$U = 43.500$.267

^a Language dominance was determined using a verbal fluency task (Woermann et al., 2003); ^b AEDs, antiepileptic drugs.

Table 2. Atrophy in predominantly right fronto-limbic and brainstem regions is associated with lower self-reported affective and cognitive empathy.

Anatomic region	L/R	Cluster volume (mm ³)	MNI coordinates			<i>t</i> -score
			x	y	z	
<i>Empathic concern (EC)</i>						
Ventromedial prefrontal cortex (BA 10)	R	127	17	56	13	3.85
Dorsomedial prefrontal cortex (BA 8)	L	98	-3	44	49	3.87
Dorsolateral prefrontal cortex (BA 44)	R	77	30	30	24	3.70
Inferior parietal lobule	L	64	-66	-51	33	3.83
Parahippocampal gyrus	R	23	29	-13	-29	3.36
<i>Perspective taking (PT)</i>						
Thalamus	R	554	11	-31	12	4.47
Midbrain	L/R	392	-5	-33	-12	4.41
Hippocampus	R	126	27	-22	-11	3.70
Parahippocampal gyrus	R	†				
Parahippocampal gyrus	R	115	26	0	-36	3.56
Fusiform gyrus	R	†				
Inferior temporal gyrus	R	70	54	-2	-42	3.62
Paracentral lobule	R	55	11	-21	72	3.77

MNI coordinates given for maximum *t*-score for each region. Results are significant at $P < .001$, uncorrected, $k = 20$. L = left; R = right. [†]Regions included in the cluster immediately above.

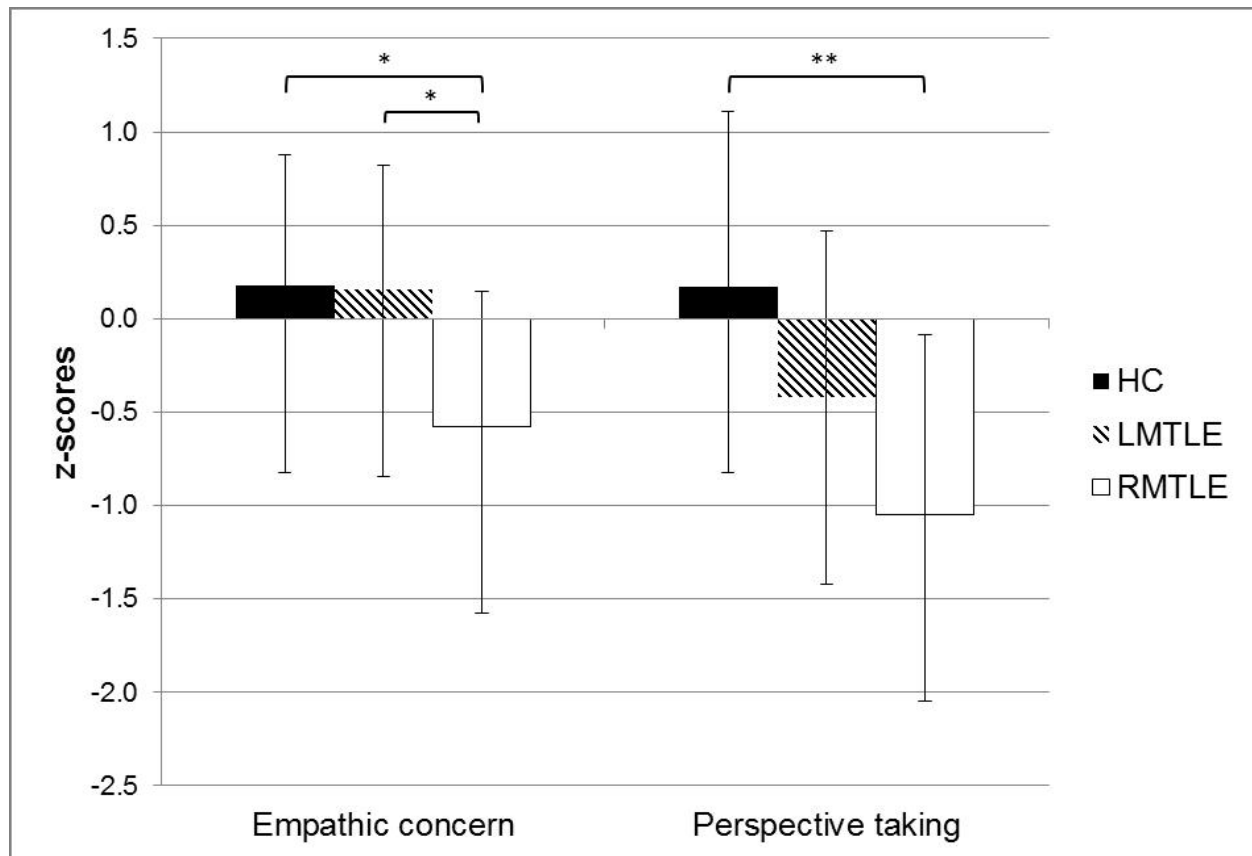


Figure 1. Standardized mean SPF scores, norm-adjusted for age and controlled for depressive symptoms, by diagnostic group (healthy controls, $n = 33$; LMTLE, $n = 9$; RMTLE, $n = 13$). The RMTLE patients reported lower empathic concern (EC) than both the healthy controls and the LMTLE patients, and lower perspective taking (PT) compared to the healthy controls. Significant group differences are denoted by $*P < .05$, $**P < .01$, FDR-corrected for multiple comparisons. Error bars represent SDs.

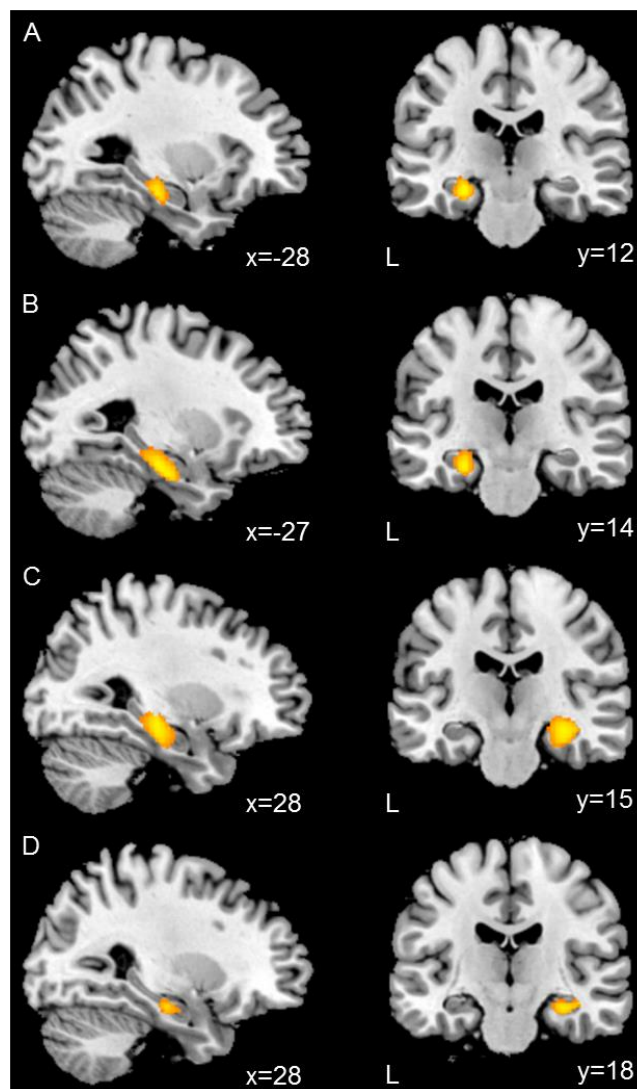


Figure 2. T-score maps showing mesial temporal atrophy in the LMTLE and RMTLE groups when controlling for age, education, total intracranial volume, and depressive symptoms. Significant volume loss was found in the left mesial temporal lobe (hippocampus, parahippocampal gyrus) of the LMTLE group when compared to (A) the healthy controls (MNI peak: $x = -27$, $y = -22$, $z = -15$, $k = 311$) and (B) the RMTLE group (MNI peak: $x = -26$, $y = -22$, $z = -17$, $k = 620$). The RMTLE group demonstrated atrophy in the right mesial temporal lobe (hippocampus, parahippocampal gyrus) when compared to (C) the healthy controls (MNI peak: $x = 32$, $y = -22$, $z = -15$, $k = 986$) and (D) the LMTLE group (MNI peak: $x = 39$, $y = -9$, $z = -15$, $k = 351$). Colored voxels show the regions in the mesial temporal lobes that were significant at $P < .0001$, uncorrected, $k = 10$. Results are overlaid on the MNI standard brain. L = left.

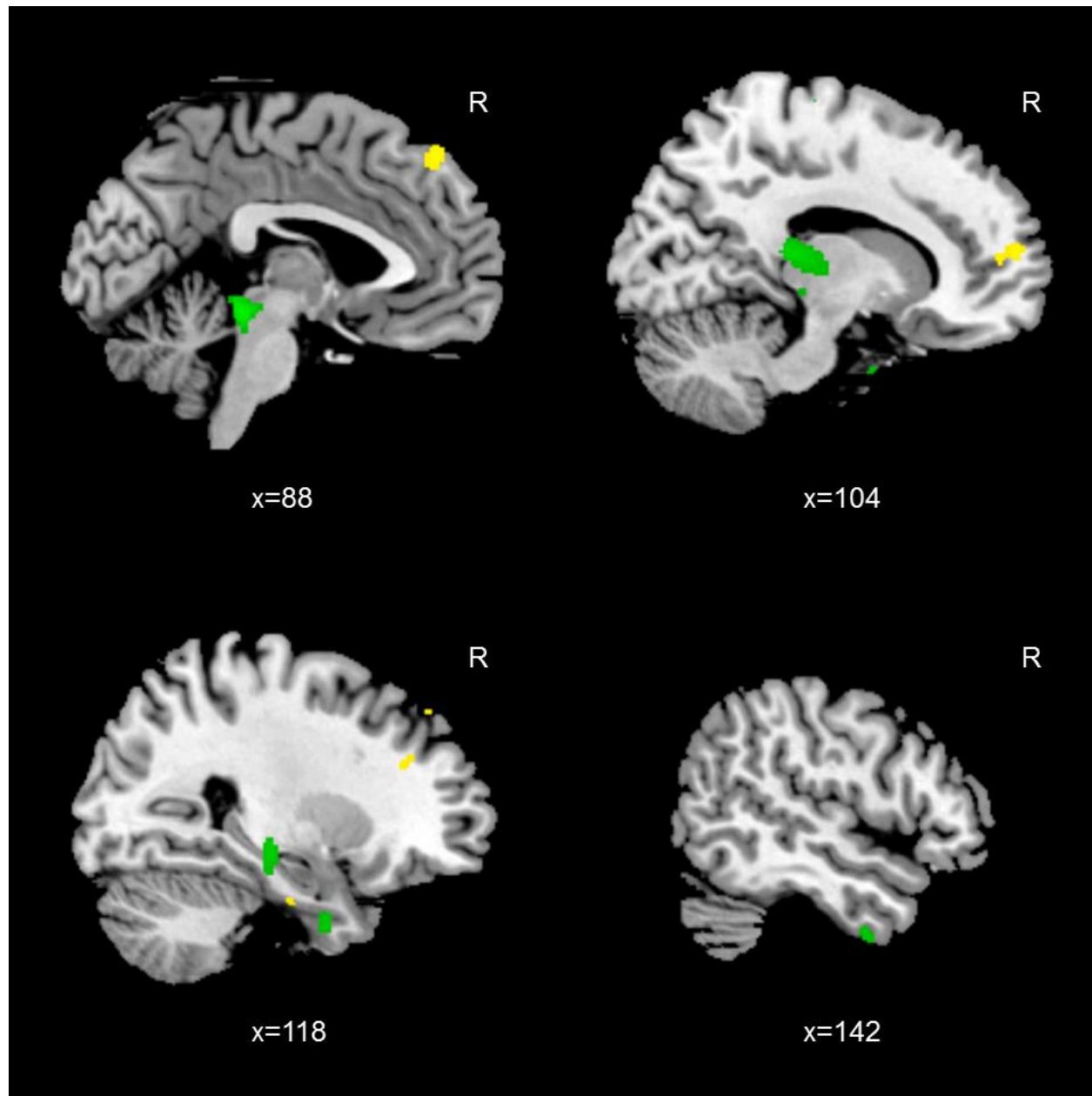


Figure 3. *T*-score maps of right fronto-limbic and brainstem regions for which atrophy was associated with lower self-reported empathic concern (EC; yellow) and perspective taking (PT; green) when controlling for age, education, total intracranial volume, and the presence of depressive symptoms ($n = 55$). Results are displayed at $P < .001$, uncorrected, $k = 20$, and are overlaid on the MNI standard brain. R = right.

References

- Aichhorn, M., Perner, J., Weiss, B., Kronbichler, M., Staffen, W., & Ladurner, G. (2009). Temporo-parietal junction activity in theory-of-mind tasks: falseness, beliefs, or attention. *Journal of Cognitive Neuroscience*, 21, 1179-1192.
- Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage*, 38, 95-113.
- Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage*, 26, 839-851.
- Banissy, M. J., Kanai, R., Walsh, V., & Rees, G. (2012). Inter-individual differences in empathy are reflected in human brain structure. *Neuroimage*, 62, 2034-2039.
- Baron-Cohen, S., & Wheelwright, S. (2004). The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorders*, 34, 163-175.
- Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Annals of Statistics*, 29, 1165-1188.
- Benuzzi, F., Meletti, S., Zamboni, G., Calandra-Buonaura, G., Serafini, M., Lui, F., . . . Nichelli, P. (2004). Impaired fear processing in right mesial temporal sclerosis: a fMRI study. *Brain Research Bulletin*, 63, 269-281.
- Bernhardt, B., Worsley, K., Kim, H., Evans, A., Bernasconi, A., & Bernasconi, N. (2009). Longitudinal and cross-sectional analysis of atrophy in pharmaco-resistant temporal lobe epilepsy. *Neurology*, 72, 1747-1754.
- Bonilha, L., Edwards, J. C., Kinsman, S. L., Morgan, P. S., Fridriksson, J., Rorden, C., . . . Halford, J. J. (2010). Extrahippocampal gray matter loss and hippocampal deafferentation in patients with temporal lobe epilepsy. *Epilepsia*, 51, 519-528.
- Bzdok, D., Schilbach, L., Vogeley, K., Schneider, K., Laird, A. R., Langner, R., & Eickhoff, S. B. (2012). Parsing the neural correlates of moral cognition: ALE meta-analysis on morality, theory of mind, and empathy. *Brain Structure and Function*, 217, 783-796.
- Carr, L., Iacoboni, M., Dubeau, M.-C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences*, 100, 5497-5502.

- Cohn, M., St-Laurent, M., Barnett, A., & McAndrews, M. P. (2014). Social inference deficits in temporal lobe epilepsy and lobectomy: risk factors and neural substrates. *Social Cognitive and Affective Neuroscience*. doi: 10.1093/scan/nsu101
- Cox, C. L., Uddin, L. Q., Di Martino, A., Castellanos, F. X., Milham, M. P., & Kelly, C. (2012). The balance between feeling and knowing: affective and cognitive empathy are reflected in the brain's intrinsic functional dynamics. *Social Cognitive and Affective Neuroscience*, 7, 727-737.
- Craig, A. B. (2009). How do you feel--now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, 10, 59-70.
- Davis, M. H. (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology*, 44, 113.
- Decety, J. (2005). Perspective taking as the royal avenue to empathy. In B. F. Malle & S. D. Hodges (editors). *Other minds: How humans bridge the divide between self and others* (p. 135-149). New York: Guilford Publications.
- Decety, J. (2011). Dissecting the neural mechanisms mediating empathy. *Emotion Review*, 3, 92-108.
- Decety, J., & Chaminade, T. (2003). Neural correlates of feeling sympathy. *Neuropsychologia*, 41, 127-138.
- Decety, J., & Jackson, P. L. (2004). The functional architecture of human empathy. *Behavioral and Cognitive Neuroscience Reviews*, 3, 71-100.
- Decety, J., & Lamm, C. (2006). Human empathy through the lens of social neuroscience. *The Scientific World Journal*, 6, 1146-1163.
- Decety, J., & Lamm, C. (2007). The role of the right temporoparietal junction in social interaction: how low-level computational processes contribute to meta-cognition. *The Neuroscientist*, 13, 580-593.
- Decety, J., & Meyer, M. (2008). From emotion resonance to empathic understanding: A social developmental neuroscience account. *Development and Psychopathology*, 20, 1053-1080.
- Decety, J., & Sommerville, J. A. (2003). Shared representations between self and other: a social cognitive neuroscience view. *Trends in Cognitive Sciences*, 7, 527-533.

- Derntl, B., Finkelmeyer, A., Toygar, T. K., Hülsmann, A., Schneider, F., Falkenberg, D. I., & Habel, U. (2009). Generalized deficit in all core components of empathy in schizophrenia. *Schizophrenia Research*, 108, 197-206.
- Eisenberg, N., & Strayer, J. (1990). *Empathy and its development*. Cambridge, MA: Cambridge University Press.
- Fan, Y., Duncan, N. W., de Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neuroscience & Biobehavioral Reviews*, 35, 903-911.
- Focke, N. K., Thompson, P. J., & Duncan, J. S. (2008). Correlation of cognitive functions with voxel-based morphometry in patients with hippocampal sclerosis. *Epilepsy & Behavior*, 12, 472-476.
- Fuerst, D., Shah, J., Shah, A., & Watson, C. (2003). Hippocampal sclerosis is a progressive disorder: a longitudinal volumetric MRI study. *Annals of Neurology*, 53, 413-416.
- Gallagher, H. L., & Frith, C. D. (2003). Functional imaging of 'theory of mind'. *Trends in Cognitive Sciences*, 7, 77-83.
- Hillis, A. E. (2014). Inability to empathize: brain lesions that disrupt sharing and understanding another's emotions. *Brain*, 137, 981-997.
- Hlobil, U., Rathore, C., Alexander, A., Sarma, S., & Radhakrishnan, K. (2008). Impaired facial emotion recognition in patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS): Side and age at onset matters. *Epilepsy Research*, 80, 150-157.
- James, W. (1884). What is an emotion? *Mind*, 9, 188-205.
- Kanner, A. M., Schachter, S. C., Barry, J. J., Hersdorffer, D. C., Mula, M., Trimble, M., . . . Caplan, R. (2012). Depression and epilepsy: epidemiologic and neurobiologic perspectives that may explain their high comorbid occurrence. *Epilepsy & Behavior*, 24, 156-168.
- Keller, S. S., Baker, G., Downes, J. J., & Roberts, N. (2009). Quantitative MRI of the prefrontal cortex and executive function in patients with temporal lobe epilepsy. *Epilepsy & Behavior*, 15, 186-195.
- Keller, S. S., & Roberts, N. (2008). Voxel-based morphometry of temporal lobe epilepsy: an introduction and review of the literature. *Epilepsia*, 49, 741-757.

- Lamm, C., Decety, J., & Singer, T. (2011). Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage*, *54*, 2492-2502.
- Lange, C. G. (1885). The mechanism of the emotions. In B. Rand (editor), *The Classical Psychologists* (p. 672-685). Boston, MA: Houghton Mifflin.
- Leigh, R., Oishi, K., Hsu, J., Lindquist, M., Gottesman, R. F., Jarso, S., . . . Hillis, A. E. (2013). Acute lesions that impair affective empathy. *Brain*, *136*, 2539-2549.
- Marsh, A. A., Stoycos, S. A., Brethel-Haurwitz, K. M., Robinson, P., VanMeter, J. W., & Cardinale, E. M. (2014). Neural and cognitive characteristics of extraordinary altruists. *Proceedings of the National Academy of Sciences*, *111*, 15036-15041.
- Meletti, S., Benuzzi, F., Cantalupo, G., Rubboli, G., Tassinari, C. A., & Nichelli, P. (2009). Facial emotion recognition impairment in chronic temporal lobe epilepsy. *Epilepsia*, *50*, 1547-1559.
- Meletti, S., Benuzzi, F., Nichelli, P., & Tassinari, C. A. (2003). Damage to the right hippocampal-amygdala formation during early infancy and recognition of fearful faces: neuropsychological and fMRI evidence in subjects with temporal lobe epilepsy. *Annals of the New York Academy of Sciences*, *1000*, 385-388.
- Meletti, S., Benuzzi, F., Rubboli, G., Cantalupo, G., Stanzani Maserati, M., Nichelli, P., & Tassinari, C. A. (2003). Impaired facial emotion recognition in early-onset right mesial temporal lobe epilepsy. *Neurology*, *60*, 426-431.
- Paulus, C. (2009). Der Saarbrücker Persönlichkeitsfragebogen SPF (IRI) zur Messung von Empathie: Psychometrische Evaluation der deutschen Version des Interpersonal Reactivity Index. Available from: <http://psydok.sulb.uni-saarland.de/volltexte/2009/2363/>.
- Perry, R., Rosen, H., Kramer, J., Beer, J., Levenson, R., & Miller, B. (2001). Hemispheric dominance for emotions, empathy and social behaviour: evidence from right and left handers with frontotemporal dementia. *Neurocase*, *7*, 145-160.
- Preston, S. D., & De Waal, F. (2002). Empathy: Its ultimate and proximate bases. *Behavioral and Brain Sciences*, *25*, 1-20.

- Rankin, K. P., Gorno-Tempini, M. L., Allison, S. C., Stanley, C. M., Glenn, S., Weiner, M. W., & Miller, B. L. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain*, *129*, 2945-2956.
- Rankin, K. P., Kramer, J. H., & Miller, B. L. (2005). Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cognitive and Behavioral Neurology*, *18*, 28-36.
- Rankin, K. P., Salazar, A., Gorno-Tempini, M. L., Sollberger, M., Wilson, S. M., Pavlic, D., . . . Miller, B. L. (2009). Detecting sarcasm from paralinguistic cues: anatomic and cognitive correlates in neurodegenerative disease. *Neuroimage*, *47*, 2005-2015.
- Salgado, P. C. B., Yasuda, C. L., & Cendes, F. (2010). Neuroimaging changes in mesial temporal lobe epilepsy are magnified in the presence of depression. *Epilepsy & Behavior*, *19*, 422-427.
- Saxe, R., & Wexler, A. (2005). Making sense of another mind: the role of the right temporo-parietal junction. *Neuropsychologia*, *43*, 1391-1399.
- Schurz, M., Aichhorn, M., Martin, A., & Perner, J. (2013). Common brain areas engaged in false belief reasoning and visual perspective taking: a meta-analysis of functional brain imaging studies. *Frontiers in Human Neuroscience*, *7*, 712.
- Sedda, A., Rivolta, D., Scarpa, P., Burt, M., Frigerio, E., Zanardi, G., . . . Francione, S. (2013). Ambiguous emotion recognition in temporal lobe epilepsy: the role of expression intensity. *Cognitive, Affective, & Behavioral Neuroscience*, *13*, 452-463.
- Shamay-Tsoory, S. G. (2011). The neural bases for empathy. *The Neuroscientist*, *17*, 18-24.
- Shamay-Tsoory, S. G., Aharon-Peretz, J., & Perry, D. (2009). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain*, *132*, 617-627.
- Shamay-Tsoory, S. G., Tomer, R., Berger, B., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *Journal of Cognitive Neuroscience*, *15*, 324-337.
- Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., Goldsher, D., & Aharon-Peretz, J. (2005). Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. *Cognitive and Behavioral Neurology*, *18*, 55-67.

- Shamay-Tsoory, S. G., Tomer, R., Goldsher, D., Berger, B., & Aharon-Peretz, J. (2004). Impairment in cognitive and affective empathy in patients with brain lesions: anatomical and cognitive correlates. *Journal of Clinical and Experimental Neuropsychology*, 26, 1113-1127.
- Shamim, S., Hasler, G., Liew, C., Sato, S., & Theodore, W. H. (2009). Temporal lobe epilepsy, depression, and hippocampal volume. *Epilepsia*, 50, 1067-1071.
- Singer, T. (2006). The neuronal basis and ontogeny of empathy and mind reading: review of literature and implications for future research. *Neuroscience & Biobehavioral Reviews*, 30, 855-863.
- Singer, T., Critchley, H. D., & Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences*, 13, 334-340.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, 303, 1157-1162.
- Sollberger, M., Stanley, C. M., Wilson, S. M., Gyurak, A., Beckman, V., Growdon, M., . . . Rankin, K. P. (2009). Neural basis of interpersonal traits in neurodegenerative diseases. *Neuropsychologia*, 47, 2812-2827.
- Szemere, E., & Jokeit, H. (2015). Quality of Life is Social—Towards an improvement of social abilities in patients with epilepsy. *Seizure*, 26, 12-21.
- Toller, G., Adhimoolam, B., Grunwald, T., Huppertz, H.-J., Kurthen, M., Rankin, K. P., & Jokeit, H. (2015). Right mesial temporal lobe epilepsy impairs empathy-related brain responses to dynamic fearful faces. *Journal of Neurology*, 262, 729-741.
- Völlm, B. A., Taylor, A. N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., . . . Elliott, R. (2006). Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *Neuroimage*, 29, 90-98.
- Woermann, F. G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., . . . Ebner, A. (2003). Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology*, 61, 699-701.
- Wood, R. L., & Williams, C. (2008). Inability to empathize following traumatic brain injury. *Journal of the International Neuropsychological Society*, 14, 289-296.

Supplementary Table 1. Etiology and seizure frequency of each MTLE patient.

Group Patient	Sex	Age	Possible etiology	Seizure frequency
LMTLE				
1	f	15	Febrile convulsions	4 focal seizures/m ^a
2	m	27	unknown	4 focal/secondary generalized seizures/m
3	m	33	Febrile convulsions	5-7 focal seizures/m
4	f	53	Febrile convulsions	1-2 focal seizures/m, rare secondary generalization
5	m	20	Perinatal hypoxia	0-2 focal seizures/d ^b
6	f	45	Febrile convulsions	1-8 focal seizures/d
7	f	50	Renal hyperintensive encephalopathy	1 focal seizure/d, rare secondary generalization
8	m	19	Febrile convulsions	25 focal seizures/m, rare secondary generalization
9	f	17	Posterior reversible encephalopathy syndrome	1-2 focal seizures/m
RMTLE				
1	m	57	Meningitis	5 focal seizures/m, rare secondary generalization
2	f	47	Mild traumatic brain injury	2 focal seizures/m
3	f	48	Meningitis	4-5 focal seizures/m, rare secondary generalization
4	m	24	Febrile convulsions	5 focal/secondary generalized seizures/m
5	f	27	Febrile convulsions	5 focal seizures/m, rare secondary generalization
6	m	48	unknown	3-4 focal seizures/d
7	m	48	unknown	1 focal seizures/m
8	m	47	Meningitis	1 focal seizures/m
9	m	37	unknown	4 focal/secondary generalized seizures/m
10	f	51	Febrile convulsions	2-3 focal seizures/m
11	f	33	Febrile convulsions	20 focal seizures/m, rare secondary generalization
12	f	61	unknown	1 focal seizure/d, rare secondary generalization
13	f	36	Febrile convulsions	1-3 focal seizures/m

LMTLE, left mesial temporal lobe epilepsy; RMTLE, right mesial temporal lobe epilepsy; m, month; d, day.

3.4 Amygdala dysfunction with preserved psychophysiological and subjective arousal in two patients with Urbach-Wiethe disease

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Abstract

Urbach-Wiethe disease (UWD) is a unique lesion model of bilateral amygdala dysfunction. However, its clinical signs vary considerably between cases. In this study, a well-validated dynamic fearful face fMRI paradigm was used in two UWD patients with incomplete bilateral amygdala damage. Changes in heart rate variability and subjective arousal were also assessed. Neither patient demonstrated activity in unaffected amygdala regions. However, their individual patterns of autonomic and subjective arousal to the faces did not generally differ from the controls. These preliminary findings indicate partly preserved physiological and psychological responses to fearful faces in two UWD cases with bilateral amygdala dysfunction.

Keywords: Urbach-Wiethe disease; amygdala, fMRI; dynamic fearful faces; heart rate variability

Introduction

A substantial body of research has demonstrated that the amygdala is a core affective region that shapes human's attention, perception, memory, and social behavior (Phelps & LeDoux, 2005; Pessoa, 2008, 2010). The most compelling evidence on the precise functions of the human amygdala comes from systematic investigations in rare cases with focal bilateral amygdala lesions due to Urbach-Wiethe disease (UWD). In line with the historical view of the amygdala as a fear module (Öhman & Mineka, 2001), various studies have demonstrated that most UWD patients are impaired on the recognition of negatively valenced emotions, particularly of fearful ones (Adolphs, Tranel, Damasio, & Damasio, 1994, 1995; Calder, 1996; Adolphs et al., 1999; Siebert, Markowitsch, & Bartel, 2003; Thornton et al., 2008; Becker et al., 2012). Consistent with this evidence, a female case with complete bilateral amygdala damage, known as patient SM, has been found to lack some of the deepest negative emotions about her past (Tranel, Gullickson, Koch, & Adolphs, 2006) and to show a generally impoverished experience of fear (Feinstein, Adolphs, Damasio, & Tranel, 2011).

Due to projections of the amygdala to various regions of the brainstem, the structure can coordinate behavioral, autonomic, and neuroendocrine responses to salient extrapersonal stimuli, including those related to fear. Therefore, the amygdala is sometimes regarded as the “controller of the brainstem” (Cardinal, Parkinson, Hall, & Everitt, 2002). Consequently, a few studies have measured UWD patients' autonomic reactivity, including skin conductance, heart rate, and acoustic startle responses during the processing of internally and externally triggered fear (Bechara et al., 1995; Feinstein et al., 2011; Becker et al., 2012; Klumpers, Morgan, Terburg, Stein, & van Honk, 2014). While some evidence suggests that UWD is associated with diminished fear-related physiological responses (Bechara et al., 1995; Becker et al., 2012; Klumpers et al., 2014), other evidence indicates that physiological responses to internally and externally triggered fear remain unaffected in UWD (Becker et al., 2012; Feinstein et al., 2013).

Previous research has shown that the presence and the degree of fear-related behavioral and autonomic impairments in UWD vary greatly from case to case (Adolphs, Russell, & Tranel, 1999; Adolphs et al., 1999). Such interindividual variability may be attributed to differences in age at lesion onset, extent of amygdala damage, presence of epilepsy, and genetic and environmental influences. Surprisingly, even identical twin sisters with focal damage largely

restricted to the basolateral amygdala have shown differing degrees of fear-related impairments (Becker et al., 2012; Mihov et al., 2013). Using functional magnetic resonance imaging (fMRI), these studies have found that only the twin with preserved fearful face recognition and intact acoustic startle responses showed residual or compensatory activity in regions of the cortical mirror neuron system during the observation of static fearful faces. These findings have led to the suggestion that the presence or absence of residual or compensatory activation in extra-amygdalar regions may at least partly account for the heterogeneous fear-related deficits found across UWD patients.

In the case of incomplete bilateral amygdala damage, the presence or absence of residual activity or adaptive functional compensation within unaffected amygdala regions may also be responsible for such interindividual differences in the processing of fear. Consistent with this assumption, Terburg et al. (2012) found that five UWD patients with damage to the basolateral amygdala exhibited increased activity in unaffected parts of the amygdala during the observation of subconsciously presented static fearful faces. Behaviorally, these patients attended longer to the eye region of dynamic fearful faces and showed increased recognition of the fearful faces than the controls. Despite the finding of increased amygdala responses in a group of five UWD patients, it remains unknown whether such residual or compensatory activation within unaffected amygdala regions occurs frequently in UWD.

Therefore, in the present multiple case study, we used a dynamic fearful face fMRI task (Schacher et al., 2006) in two UWD patients with incomplete amygdala damage and in three matched healthy controls. This paradigm has previously been shown to reliably induce activity in the bilateral amygdala of individual healthy Caucasians. The task has also been applied to patients with mesial temporal lobe epilepsy (MTLE) and has been demonstrated to be a valid method to lateralize unilateral MTLE (MTLE; Schacher et al., 2006; Broicher et al., 2012; Toller et al., 2015). Language dominance was also determined, because of previous evidence showing right-hemisphere predominance for the processing of negative emotions (Adolphs, Damasio, Tranel, & Damasio, 1996; Borod et al., 1998; Craig, 2005). The primary aim of the current study was to investigate whether two UWD patients with incomplete amygdala damage would show activity in unaffected amygdala regions in response to consciously presented dynamic fearful faces. In addition, their changes in heart rate variability (HRV) and their subjective arousal was

assessed during the observation of the faces outside the scanner and were compared with the results of a matched healthy control group ($n = 7$). The inclusion of HRV measures was based on the top-down control of the amygdala on autonomic brainstem regions that control cardiovascular functions. Moreover, HRV was measured because of our recent findings showing that the dynamic fearful face task was associated with midbrain periaqueductal gray (PAG) responses in a group of healthy Caucasians (Toller et al., 2015). Because of the incomplete bilateral amygdala damage in our two UWD patients, we expected that their autonomic responses to dynamic fearful faces would at least be partly preserved.

Methods

Participants

We studied two women of mixed ancestry with UWD who were recruited from a previously described cohort living in the rural and impoverished Northern Cape province of South Africa, with no history of epileptic seizures and of psychiatric comorbidities (Terburg et al., 2012). Each patient's demographic and clinical data are presented in Table 1 (p. 118), and their bilateral amygdala calcifications are shown in Figure 1 (p. 125). Both patients' assessments were conducted in their native language Afrikaans. To compare the fearful face fMRI of each UWD patient with that of individual control subjects, three healthy women were recruited (Controls 1-3 in Table 1, p. 118) who were matched for age, education (IQ within the normal range), and ethnicity (people of mixed ancestry). Four additional female controls (Controls 4-7 in Table 1, p. 118) who were also matched for age, education (IQ within the normal range), and ethnicity were included to obtain group reference data ($n = 7$) for each patient's HRV measures. Based on clinical interviews and structural MRI, all healthy controls were free of current or previous neurological or psychiatric disorders, alcohol or substance abuse, and chemotherapy. The control subjects were tested in English. All patients and controls provided written informed consent. The study was approved by the human ethics committee of the University of Cape Town and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Functional imaging

Fearful face paradigm

The fMRI task used in this study was previously validated in healthy controls and in patients with unilateral MTLE (Schacher et al., 2006). In brief, the paradigm consisted of 16 alternating activation and baseline blocks each lasting 24 seconds. During the activation conditions, a total of 75 brief (2-3 seconds) episodes selected from thriller and horror movies were presented. All episodes showed faces of actors expressing intense fear, but no violence or aggression. During the baseline conditions, 72 short video recordings of local landscapes were shown. The stimuli were presented on a screen using a projector and were viewed through an overhead mirror. The participants were told that they would see brief episodes of dynamic fearful faces alternating with landscape scenes. They were instructed to relax and to focus on the actors' eyes.

Language paradigm

Language dominance was established using a verb generation task that has been well-validated in a cohort of epilepsy patients (Ives-Deliperi, Butler, & Meintjes, 2013). The task began with a 20 s rest period followed by 10 alternating rest and active 20 s blocks to total 3:40 minutes. In the active condition of the verb generation task, nouns were presented at 3 s intervals (7 per block) and the patients were required to think of a verb semantically related to the noun (i.e. 'what to do with'). Patients were instructed to generate the verb silently and not to mouth the word or speak, in order to restrict motion artifact. Stimuli in the control condition consisted of high and low tones to engage auditory processing and attention.

Image acquisition

Structural and functional MRI scans were acquired on a 1.5-T Siemens Avanto scanner (Erlangen, Germany) using a 20-channel head coil. A T1-weighted 3D inversion recovery gradient echo sequence was used to obtain the structural images (160 sagittal slices, 1.2-mm thick, skip = 0 mm; repetition time = 2400 ms; echo time = 3.61 ms; flip angle = 8°; field of view = 240 x 240 mm²; voxel size = 1.3 x 1.3 x 1.2 mm; matrix size = 192 x 192). The functional scans of the fearful face task were obtained using a gradient echo planar imaging sequence (repetition time = 1530 ms; echo time = 60 ms; flip angle = 90°; field of view = 220 x 220 mm²; voxel size = 3.4 x 3.4 x 5

mm; matrix size = 64 x 64). Twelve coronal slices (5-mm thick, skip = 0.5 mm) were acquired orthogonal to the hippocampal formation and were spread over the temporal lobe. The functional scans of the language task were also obtained using a gradient echo planar imaging sequence (repetition time = 2000 ms; echo time = 50 ms; flip angle = 90°; field of view = 220 x 220 mm²; voxel size = 3.4 x 3.4 x 5 mm; matrix size = 64 x 64). Twenty-one axial slices (5-mm thick, skip = 0.5 mm) were acquired parallel to the anterior-posterior commissure (AC-PC line). Foam padding was used to reduce head motion.

Image preprocessing and analyses

Functional imaging data of the fearful face task were analyzed using Statistical Parametric Mapping (SPM)8 (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007). After discarding the first 16 volumes to allow for magnetic field stabilization, functional images were realigned, co-registered, normalized to the MNI template and re-sampled at a voxel size of 2 mm³, and smoothed with a 4mm full-width at half-maximum Gaussian kernel. To remove low-frequency drifts, high pass temporal filtering with a cut-off of 128 s was applied. To create regressors of interest, each subject's time series of both conditions (fearful faces/landscapes) were modelled by SPM8's canonical hemodynamic response function, with each participant's six estimated motion parameters included as regressors of no interest. For each subject, contrast images were calculated by applying the contrast fearful faces > landscapes to the parameter estimates. A peak threshold of $P < .001$, uncorrected, and an extent threshold of 25 contiguous voxels (2 x 2 x 2 mm) were applied to the contrast fearful faces > landscapes of each subject.

Functional imaging analysis of the language task was performed using Brain Voyager QX (Brain Innovation, Maastricht, The Netherlands; Goebel, Esposito, & Formisano, 2006). After discarding the first two volumes, each subject's functional image was slice-time corrected, realigned, co-registered to the native T1 image, re-sampled at a voxel size of 3 mm³, and smoothed with a 4mm full-width at half-maximum Gaussian kernel. To remove low-frequency drifts, high pass temporal filtering with a low cut-off of 3 cycles per run was applied.

Electrocardiogram (ECG) outside the scanner

The subjects' ECG was measured prior (at rest) and during the fearful face movie (fearful face/landscape condition) presented outside the scanner. The skin surface was cleaned before the ECG electrodes were attached. ECG activity was recorded using Acqknowledge 4.1 software (Biopac Systems Inc.), sampled at 1000 Hz, and band-pass filtered between 0.5-0.35 Hz. The filtered ECG recording tachograms were visually inspected to determine the correct recognition of QRS complexes. Missed and ectopic beats were corrected.

ECG data analysis was performed using Kubios HRV analysis software (Biosignal Analysis and Medical Imaging Group, Department of Applied Physics, University of Kupio, Finland). HRV power spectrum analyses were conducted on a 3.2-minute period at rest (minute 1 to minute 4.2 at rest, measured immediately before the fearful face movie), on the 3.2-minute period of the fearful face condition (the time of the 8 fearful face blocks was added up), and on the 3.2-minute period of the landscape condition (the time of the 8 landscape blocks was added up). Thus, the inter-beat (R-R) interval tachograms that were derived from the ECG signal traces at rest, and during the fearful face condition, and during the landscape condition were each detrended. The low (LF; 0.04-0.15 Hz) and high (HF; 0.15-0.40 Hz) frequency components of the R-R intervals were estimated using an autoregressive (AR) model with an AR model order of 19 and an interpolation rate of 5 Hz. The peak frequencies and the corresponding power values were calculated for both the LF and the HF domain. To investigate whether the HF peak and the LF and HF power values of the control group differed between the state of rest, the fearful face condition, and the landscape condition, non-parametric Wilcoxon tests were performed. The mean HRV frequency domain variables of the control group were used as reference data to qualitatively interpret the HF peak and the LF and HF power values of each patient.

Post-fMRI self-ratings

After the fMRI scanning (Controls, $n = 3$) and the ECG measures (Controls, $n = 7$), 24 selected scenes of the fearful face movie were presented. After each scene, the subjects were asked to indicate on a 7-point Likert scale how arousing (1 = not arousing at all, 7 = very arousing) and how unpleasant (1 = not unpleasant at all, 7 = very unpleasant) they experienced the corresponding scene. The mean arousal and the mean unpleasantness ratings of the control

group ($n = 7$) were used as reference data to qualitatively interpret each patient's mean self-ratings.

Results

Fearful face fMRI

Controls

The activity patterns of each control subject are shown in Tables 2-4, pp. 119-121. Despite the presence of interindividual differences in the set of brain regions recruited, all three control subjects demonstrated activity in the bilateral temporal and frontal lobes. The regions included the amygdala, the superior and middle temporal gyri, the fusiform gyrus, the precentral gyrus, the superior, inferior, and middle frontal gyri, and the supplementary motor cortex (SMA) ($P < .001$, uncorrected, $k = 25$). Figure 2 (p. 126) displays the bilateral amygdala activation found in each control subject.

UWD patients

In contrast to the three control subjects, neither patient demonstrated activity in the right or left amygdala ($P < 0.001$, uncorrected, $k = 25$; Figure 3, p. 127). However, consistent with the activity patterns found in the three control subjects, patient 1 showed significant clusters in the right middle and inferior frontal gyri, bilateral precentral gyrus, the right fusiform gyrus, the left supramarginal gyrus, the right superior temporal gyrus, and the left inferior frontal gyrus ($P < .001$, $k = 25$; Table 5, p. 122). Similarly, in patient 2, significant BOLD increases were shown in the bilateral precentral gyrus, the right inferior frontal gyrus, the right fusiform gyrus, the bilateral SMA, the right middle temporal gyrus, the left postcentral gyrus, the left rolandic operculum, the left middle frontal gyrus, the right superior temporal gyrus, the left cerebellum, and the right thalamus ($P < .001$, uncorrected, $k = 25$; Table 6, p. 123).

Language fMRI

Left hemisphere language dominance was established in each patient and in each control subject ($n = 3$; Figure 4 A-E, p. 128).

ECG outside the scanner***Controls***

The mean LF and HF power did not differ between the state of rest, the fearful face condition, and the landscape condition ($P > 0.05$; Table 7, p. 124). A significant increase of the HF peak was found from the state of rest to the fearful face condition ($T = -2.37$, $P = .01$, one-tailed), and from the state of rest to the landscape condition ($T = -2.37$, $P = .01$, one-tailed).

UWD patients

In patient 1, the HF peak and the power values in the LF and HF frequency bands at rest were higher than those obtained in the control group and in patient 2 (Table 7, p. 124). Each patient's HF peak for the fearful face and the landscape condition fell within the minimum-maximum range of the control subjects. Both the LF and HF power of patient 1 were higher at rest than during both the fearful face and the landscape condition. As for the controls, comparable LF and HF power values were demonstrated for the fearful face and the landscape condition in patient 1. The LF and HF power at rest, during the fearful face condition, and during the landscape condition of patient 2 were comparable to the power values found in the controls.

Figure 5 (p. 129) shows each control subject's and each patient's individual HF peak frequency at rest, during the fearful face condition, and during the landscape condition. The results demonstrate that the patterns of patient 1 (subject 8) and patient 2 (subject 9) do not generally differ from the patterns of the individual control subjects (subjects 1-7).

Post-fMRI self-ratings

In the control group, the mean arousal of the 24 fearful face scenes was 4.40 ($SD = 1.92$) on the 7-point Likert Scale (1 = not arousing at all, 7 = very arousing). Similarly, a mean of 4.50 ($SD = 1.83$) was found for the corresponding unpleasantness ratings (1 = not unpleasant at all, 7 = very unpleasant). Interestingly, patient 1 experienced the scenes more arousing ($M = 6.75$) and more unpleasant ($M = 6.75$) than the control subjects. By contrast, patient 2 rated the scenes less arousing ($M = 2.71$) and less unpleasant ($M = 2.33$) than the controls. Figure 6A (p. 130) shows the corresponding means obtained in the control group and in each patient. However,

considering each control subjects' individual scores, it becomes evident that the ratings of each UWD patient do not generally deviate from the ratings of the control subjects (Figure 6B, p. 130).

Discussion

The aim of the present multiple case fMRI study was to investigate the impact of incomplete bilateral amygdala damage in two UWD patients on the function of unaffected amygdala regions, the changes in HRV and the subjective assessment of emotional arousal. Therefore, a well-validated dynamic fearful face fMRI task was used that has been clearly demonstrated to induce activity in the bilateral amygdala of individual healthy Caucasians. The patients' results were compared with three healthy control subjects who were matched for age, sex, education, and ethnicity. It was further examined whether incomplete bilateral amygdala damage would be associated with altered autonomic and subjectively perceived arousal during the observation of the fearful faces outside the scanner. Our results show that neither patient demonstrated activity in the unaffected parts of the amygdala. By contrast, bilateral amygdala responses were found in each of the three control subjects. Despite their bilateral amygdala damage and dysfunction, neither patient's HRV patterns generally differed from those of the healthy controls during the observation of the dynamic fearful faces. In line with these findings, the patients' arousal and unpleasantness ratings of the fearful face scenes were comparable to the healthy controls.

The bilateral amygdala responses to the dynamic fearful faces we found in three individual women of mixed ancestry confirm our previous results obtained in individual healthy Caucasians (Schacher et al., 2006). This consistent evidence from individual subjects with different ethnic backgrounds suggests that the validity of the fearful face task to map the bilateral amygdala is independent of the subjects' ethnicity. Because the patients' age, sex, education, and ethnicity did not differ from the healthy controls, their lack of activity in unaffected amygdala regions cannot be attributed to differences in these demographic variables. In the presence of left-hemisphere language dominance, each control subject demonstrated stronger activity in the right than in the left amygdala. These single case results confirm our previous group findings in healthy Caucasians and in patients with unilateral MTLE (Toller et al., 2015), and support current

models suggesting a right-hemisphere predominance for the processing of negative emotions (Adolphs et al., 1996; Borod et al., 1998; Craig, 2005).

The overall activity pattern found in extra-amygdalar regions of the healthy controls was relatively heterogeneous. However, overlapping activation was found predominantly in right lateral frontal and lateral temporal regions that are involved in action and motion perception. These regions are suggested to have been evoked by the dynamic nature of the stimulus material used in the present study. Despite the lack of amygdala responses in both UWD patients, the activity pattern in extra-amygdalar regions was very similar to that found in the control subjects. This finding is in line with previous evidence from UWD cases with incomplete bilateral amygdala damage showing preserved and even superior activity in mirror neuron regions during the observation of static and dynamic fearful faces (Becker et al., 2012; Mihov et al., 2013). In conjunction with the result that both UWD patients showed activity in the right fusiform gyrus, our findings indicate that the patients processed the faces in a similar way as the controls. Overall, the lack of amygdala responses to dynamic fearful faces is consistent with most studies showing an association of UWD with fear-related impairments, including facial emotion recognition, fear experience, and fear-related physiological responses (e.g., Adolphs et al., 1994; Bechara et al., 1995; Siebert et al., 2003; Tranel et al., 2006; Thornton et al., 2008; Feinstein et al., 2011; Becker et al., 2012; Klumbers et al., 2014).

Cortico-amygdala pathways that are recruited during fear processing indirectly modulate parasympathetic and sympathetic nervous activity through their brainstem projections, which results in state-dependent variations of cardiac activity (Davis, 1992; LeDoux, 1996; Price, 1999; Cardinal et al., 2002; Critchley et al., 2003). The LF power in the cardiac spectrogram is related to baroreflex feedback regulation rather than to cardiac sympathetic activity (Fourie et al., 2011; Rahman, Pechnik, Gross, Sewell, & Goldstein, 2011). The HF component of HRV is also of parasympathetic origin and is mediated via respiratory sinus arrhythmia (Berntson et al., 1997; Montano, Porta, & Malliani, 2001). The HF peak of the control group ($n = 7$), which is a marker of the breathing rate (Hirsch & Bishop, 1981), was higher during the processing of fearful faces and the processing of landscapes than during the resting state. Based on the evidence that the amygdala indirectly controls breathing rate, this increased autonomic arousal during the

processing of dynamic fearful faces and the processing of landscapes is indicative of increased autonomic processing during both fearful faces and landscapes versus at rest.

Despite the lack of amygdala responses to dynamic fearful faces, the qualitative pattern of LF and HF increases and decreases across the different conditions was similar between the UWD patients and the control group. This finding of comparable autonomic fear-related responses between the patients and the control group is consistent with the patients' arousal and unpleasantness ratings that did not generally differ from the ratings of the individual control subjects. This pattern of results indicates that the lack of residual or compensatory activity in unaffected parts of the amygdala during the observation of dynamic fearful faces is not necessarily associated with absent autonomic and subjective arousal responses to the faces outside the scanner. Moreover, the interindividual differences we found in autonomic and subjectively perceived arousal between the two UWD patients support the general notion that fear-related impairments vary greatly within the population of UWD (Adolphs et al., 1999; Adolphs et al., 1999; Becker et al., 2012). The present psychophysiological findings are consistent with studies in UWD cases with incomplete bilateral amygdala damage that reported preserved physiological responses, including HRV, respiration, and skin conductance, to fearful faces and to internally triggered fear (Becker et al., 2012; Feinstein et al., 2013).

The converging results from HRV and self-ratings suggest that cortical regions such as the anterior cingulate cortex and possibly also unaffected parts of the amygdala (LeDoux, 1996; Cardinal et al., 2002; Critchley et al., 2003) may be sufficient to activate brainstem regions that generate the physiological responses to fear-related stimuli. But in the light of the previous finding of diminished acoustic startle-responses in UWD cases with incomplete bilateral amygdala damage (Becker et al., 2012; Klumpers et al., 2014), this interpretation seems to be less plausible. These apparently inconsistent findings, however, are not directly comparable due to the different methodologies used across studies. Moreover, they may also be partly attributable to the considerable interindividual variability of fear-related impairments in UWD. Because HRV was measured outside the scanner in the present study, no conclusions can be drawn with regard to the direct correspondence between amygdala reactivity and changes in HRV during the processing of dynamic fearful faces. This issue needs to be addressed in future research by simultaneous recordings of fMRI and HRV.

Overall, the present study demonstrates that two UWD cases with incomplete bilateral amygdala damage show a lack of activity within unaffected parts of the amygdala during the observation of dynamic fearful faces. However, despite the presence of bilateral amygdala damage and dysfunction, their patterns of autonomic and subjective arousal in response to the faces outside the scanner were not significantly different from those of the matched control group. These results indicate that brain regions generating physiological responses to fear-related stimuli were at least partly preserved in the patients. The present neurobehavioral and psychophysiological findings support previous evidence that the disorder is associated with an interindividually varying endophenotype and is therefore not a uniform model of amygdala lesion and dysfunction.

Acknowledgments

The authors acknowledge Jack van Honk and Barak Morgan for their support and the radiology team at Mediclinic Constantiaberg, Cape Town, for technical assistance during fMRI acquisition.

Disclosure statement

The authors have no conflict of interest to disclose.

Funding

This work was supported by the Swiss Epilepsy Foundation.

Table 1. Demographic and clinical information for each subject.

Group Subject	Age	Sex	IQ		
			VIQ	PIQ	FSIQ
UWD					
1	40	f	93	85	87
2	54	f	82	84	81
Controls					
1	47	f	98	103	100
2	42	f	103	106	106
3	43	f	106	134	121
4	41	f	75	99	87
5	44	f	90	102	96
6	51	f	98	96	97
7	53	f	90	81	84

VIQ, Verbal IQ ; PIQ, Performance IQ; FSIQ, Full Scale IQ.

Table 2. Activity pattern elicited in control subject 1.

Anatomic region	L/R	Cluster size	MNI coordinates			<i>t</i> -score
			x	y	z	
Superior temporal gyrus	R	669	46	-32	2	19.15
Inferior frontal gyrus	R	523	42	10	26	10.92
Precentral gyrus	L	679	-44	6	30	10.52
Inferior frontal gyrus	L	†	-40	16	32	
Middle frontal gyrus	L	†	-48	24	34	
Superior temporal gyrus	L	106	-44	-40	-14	10.22
Fusiform gyrus	R	36	40	-40	-16	10.03
Middle frontal gyrus	R	477	40	2	60	8.88
Parahippocampal gyrus	R	48	32	-10	-30	5.81
Middle temporal gyrus	L	54	-64	-36	0	5.74
Hippocampus	R	49	24	-14	-16	5.68
Cerebellum	L	172	-2	-42	-32	5.54
Brainstem	L	†	-2	-36	-42	
Superior medial frontal gyrus	L	79	-4	50	52	5.51
Superior medial frontal gyrus	R	†	10	48	52	
Rolandic operculum	R	82	48	-26	18	5.37
Temporal pole	L	82	-48	18	-14	5.30
Caudate nucleus	L	119	-4	16	-2	5.16
Subgenual ACC	L	†	-6	26	-4	
Amygdala (SF)	R	26	16	-8	-10	5.01
Thalamus	L	63	-4	-26	6	4.73
Midbrain	R	39	12	-28	-10	4.73
Amygdala (SF)	L	49	-18	-10	-10	4.71
Supramarginal gyrus	L	28	-54	-24	16	4.64
Rolandic operculum	L	30	-40	-22	20	4.50
Superior frontal gyrus	L	33	-24	38	48	3.72

MNI coordinates given for maximum *t*-score for each cluster. Results are significant at $P < .001$, uncorrected, $k = 25$. L = left; R = right. SF, superficial nucleus. † Regions included in the cluster immediately above.

Table 3. Activity pattern elicited in control subject 2.

Anatomic region	L/R	Cluster size	MNI coordinates			<i>t</i> -score
			x	y	z	
Precentral gyrus	R	2024	42	4	32	12.63
Middle temporal gyrus	R	238	56	-18	-10	5.29
Inferior frontal gyrus	L	329	-38	12	26	7.55
Precentral gyrus	L	168	-48	-6	44	5.95
SMA	R	258	6	12	56	5.66
SMA	L	[†]	-2	-2	58	
Amygdala (SF)	R	89	16	-6	-18	5.49
Middle temporal gyrus	L	35	-50	-30	-4	4.26
Supramarginal gyrus	R	29	58	-22	26	4.18
Amygdala (LB)	L	27	-20	-6	-14	3.92
Amygdala (SF)	L	[†]	-18	-4	-22	

MNI coordinates given for maximum *t*-score for each cluster. Results are significant at $P < .001$, uncorrected, $k = 25$. LB, basolateral nucleus; SF, superficial nucleus; L = left; R = right. [†]Regions included in the cluster immediately above.

Table 4. Activity pattern elicited in control subject 3.

Anatomic region	L/R	Cluster size	MNI coordinates			<i>t</i> -score
			x	y	z	
Inferior frontal gyrus	R	3412	54	18	24	15.93
Middle temporal gyrus	R	†	42	14	54	
Fusiform gyrus	L	216	-42	-40	-24	14.97
Cerebellum	L	†	-32	-32	-30	
Precentral gyrus	L	582	-38	0	44	9.24
Fusiform gyrus	R	31	42	-34	-22	8.12
Cerebellum	R	†	48	-38	-30	
Rolandic operculum	L	657	-62	4	6	7.07
Inferior frontal gyrus	L	†	-48	20	-8	
Superior medial gyrus	R	225	6	54	42	6.86
Amygdala (SF)/Hippocampus	R	222	16	-10	-16	6.54
Parahippocampal gyrus	R	†	24	4	-26	
Middle frontal gyrus	R	260	38	50	18	4.90
Thalamus	R	102	8	-2	8	5.17
Amygdala (SF)	L	204	-26	0	-16	4.60
Inferior frontal gyrus	R	26	48	32	-14	4.48

MNI coordinates given for maximum *t*-score for each cluster. Results are significant at $P < .001$, uncorrected, $k = 25$. SF, superficial nucleus; L = left; R = right. † Regions included in the cluster immediately above.

Table 5. Activity pattern elicited in UWD patient 1.

Anatomic region	L/R	Cluster size	MNI coordinates			<i>t</i> -score
			x	y	z	
Middle frontal gyrus	R	1080	34	0	54	9.72
Precentral gyrus	R	[†]	48	0	36	
Fusiform gyrus	R	67	38	-44	-24	7.92
Precentral gyrus	L	369	-52	-4	48	7.31
Supramarginal gyrus	L	53	-60	-24	40	5.25
Inferior frontal gyrus	R	57	52	30	22	4.62
Superior temporal gyrus	R	41	48	-28	-4	4.43
Inferior temporal gyrus	L	43	-42	-32	-18	4.24

MNI coordinates given for maximum *t*-score for each cluster. Results are significant at $P < .001$, uncorrected, $k = 25$. L = left; R = right. [†]Regions included in the cluster immediately above.

Table 6. Activity pattern elicited in UWD patient 2.

Anatomic region	L/R	Cluster size	MNI coordinates			<i>t</i> -score
			x	y	z	
Precentral gyrus	R	2001	48	6	40	11.37
Inferior frontal gyrus	R	[†]	48	16	20	
Fusiform gyrus	R	46	40	-40	-18	8.18
SMA	R	395	8	14	56	7.29
Middle temporal gyrus	R	173	62	-8	-16	6.95
Precentral gyrus	L	250	-40	0	52	6.27
Postcentral gyrus	L	97	-58	-16	34	6.10
Rolandic operculum	L	303	-62	2	6	6.09
Middle frontal gyrus	L	107	-40	38	36	5.61
Superior temporal gyrus	R	56	50	-28	2	5.44
Cerebellum	L	39	-40	-50	-38	5.10
Thalamus	R	42	14	-28	4	3.91
SMA	L	26	-6	10	56	4.05

MNI coordinates given for maximum *t*-score for each cluster. Results are significant at $P < .001$, uncorrected, $k = 25$. SMA, supplementary motor cortex; L = left; R = right. [†]Regions included in the cluster immediately above.

Table 7. Heart rate variability (HRV) frequency domain variables for controls ($n = 7$) and for each UWD patient.

HRV variables	State of rest			Landscape condition					
	Controls ($n=7$)	UWD 1	UWD 2	Controls ($n=7$)	UWD 1	UWD 2	Controls ($n=7$)	UWD 1	UWD 2
LF peak ^a	0.0965	0.1367	0.1250	0.1141*	0.1172	0.1445	0.1010**	0.1211	0.1211
(range)	(0.0742-0.1250)			(0.0938-0.1484)			(0.0820-0.1211)		
HF peak ^a	0.2671	0.3125	0.2539	0.2941*	0.2930	0.2617	0.2907*	0.3047	0.2623
(range)	(0.2109-0.3500)			(0.2500-0.3500)			(0.2344-0.3633)		
LF power ^b	5.30	7.24	4.86	5.14	6.88	5.06	5.21	6.91	4.97
(range)	(4.04-6.84)			(4.14-5.91)			(4.17-6.48)		
HF power ^b	5.40	7.43	5.60	5.47	6.95	5.83	5.45	6.73	5.45
(range)	(3.33-6.65)			(3.78-6.98)			(3.56-7.21)		

LF, low frequency; HF, high frequency. ^a All LF and HF peaks are indicated in Hz (s^{-1}). ^b All LF and HF power values refer to the natural logarithm ($\ln.msec^2$). * In the controls, Wilcoxon test demonstrated significant differences between the fearful face/landscape condition and the state of rest, and ** between the landscape condition and the fearful face condition (all $P < .05$, one-tailed).

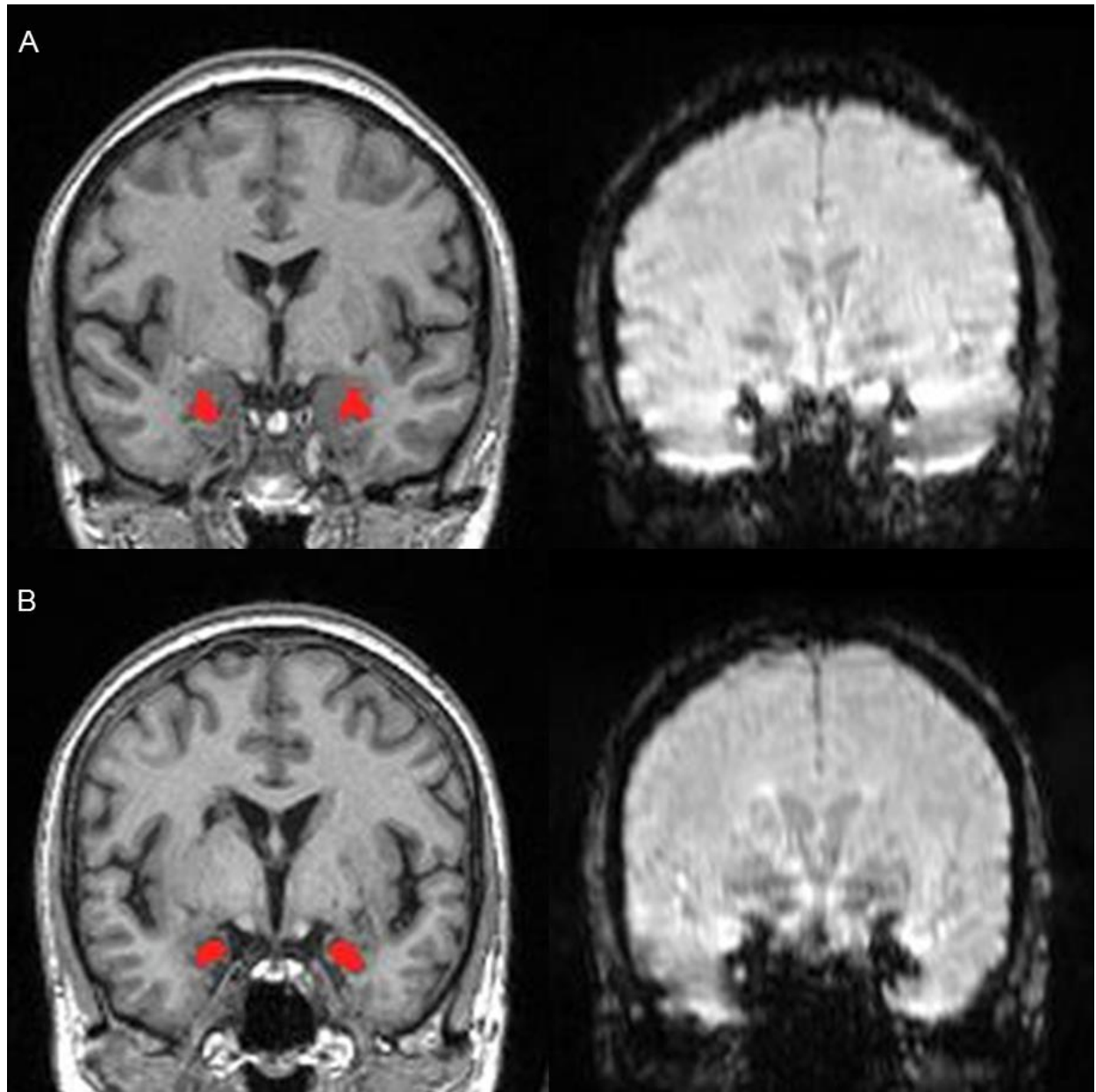


Figure 1. Structural MRI data demonstrating incomplete bilateral amygdala lesions of each UWD patient. Co-registered T1 and SWI (susceptibility-weighted imaging) images, normalized to MNI space. For patient 1 (A), the bilateral amygdala calcifications were segmented in the SWI image and were then projected to the T1 image. For patient 2 (B), the calcifications were directly segmented in the T1 image as they were less visible on the SWI image due to the blooming effect. The images display the coronal sections with the largest extent of lesions.

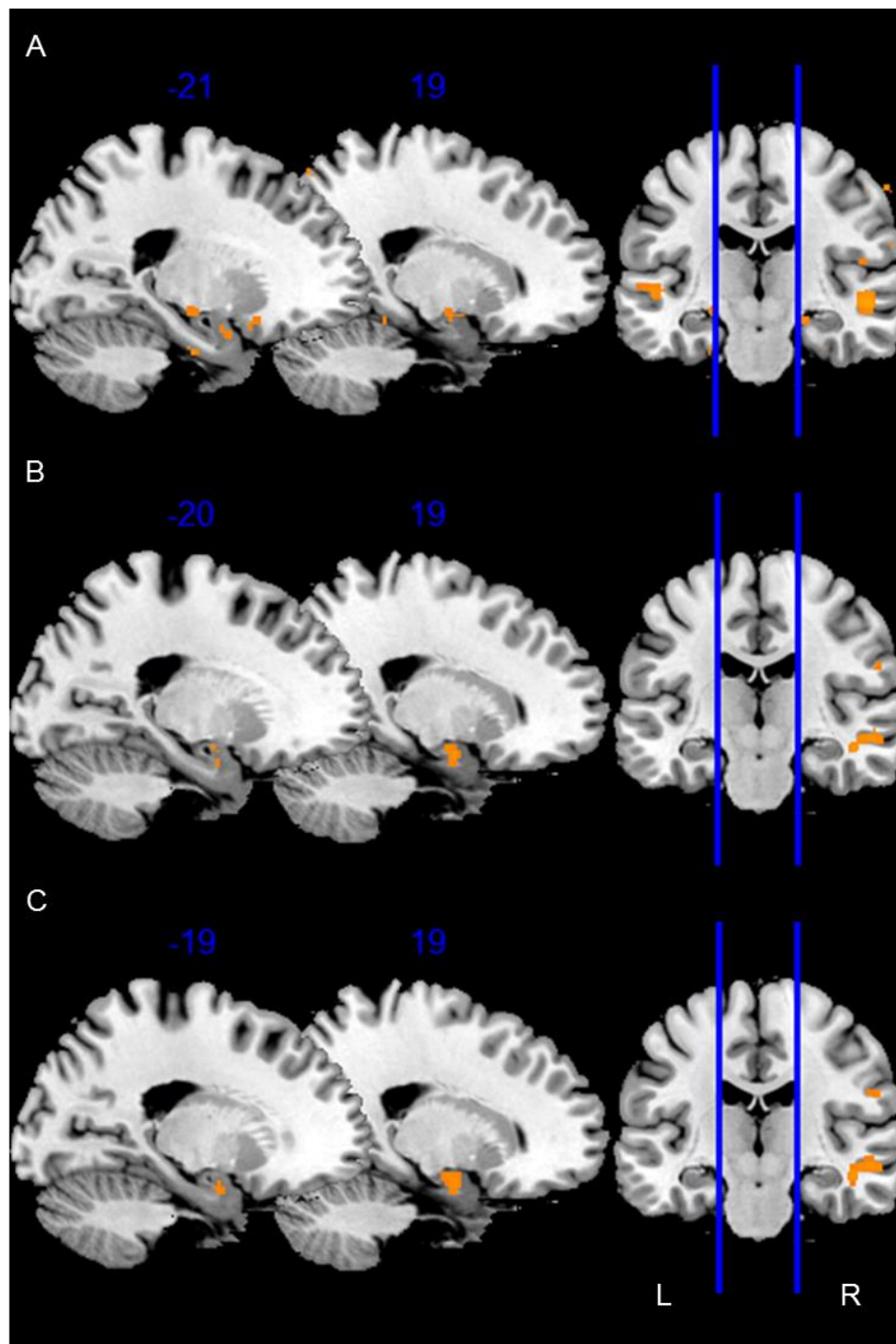


Figure 2. Amygdala responses to dynamic fearful faces in each control subject ($n = 3$). T -score maps (fearful faces > landscapes) showing increased activity in the bilateral amygdala of (A) control subject 1, (B) control subject 2, and (C) control subject 3. The statistical maps are shown at $P < .001$, uncorrected, $k = 25$. Coordinates refer to MNI space. L = left; R = right.

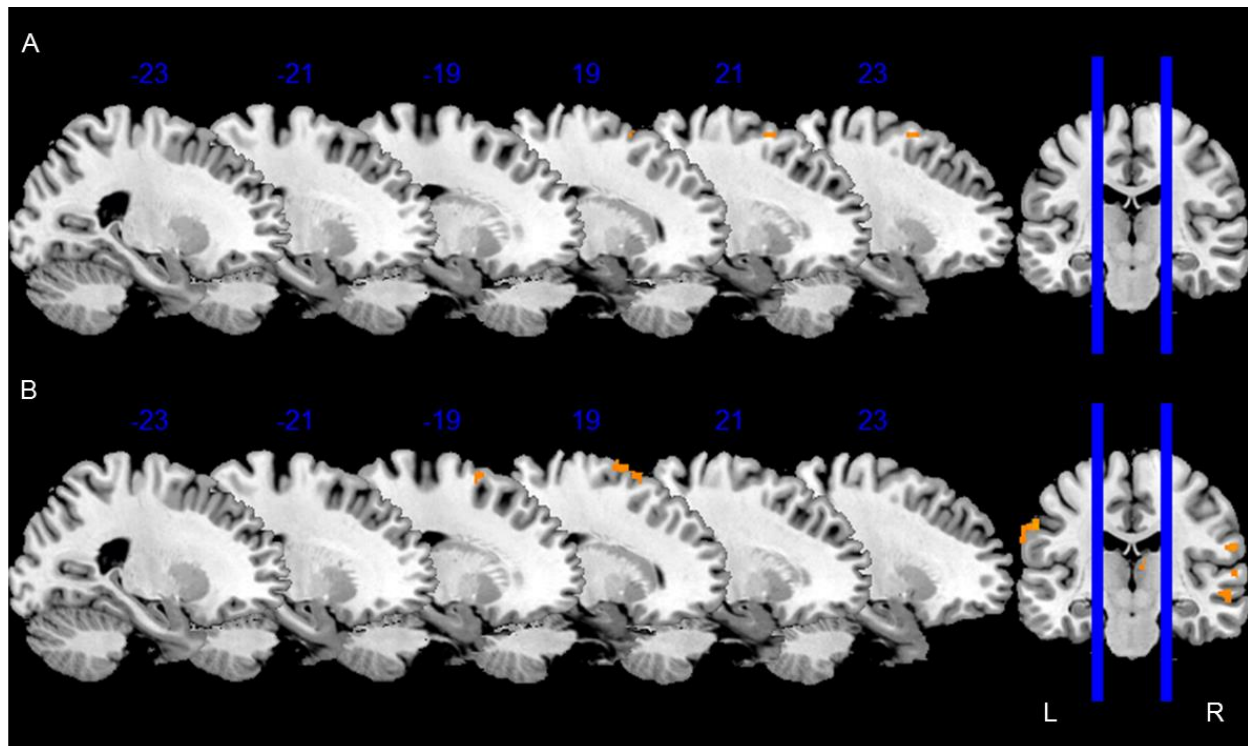


Figure 3. Lack of amygdala responses to dynamic fearful faces in each UWD patient. *T*-score maps (fearful faces > landscapes) showing no amygdala activity in (A) UWD patient 1, and in (B) UWD patient 2. The statistical maps are shown at $P < .001$, uncorrected, $k = 25$. Coordinates refer to MNI space. L = left; R = right.

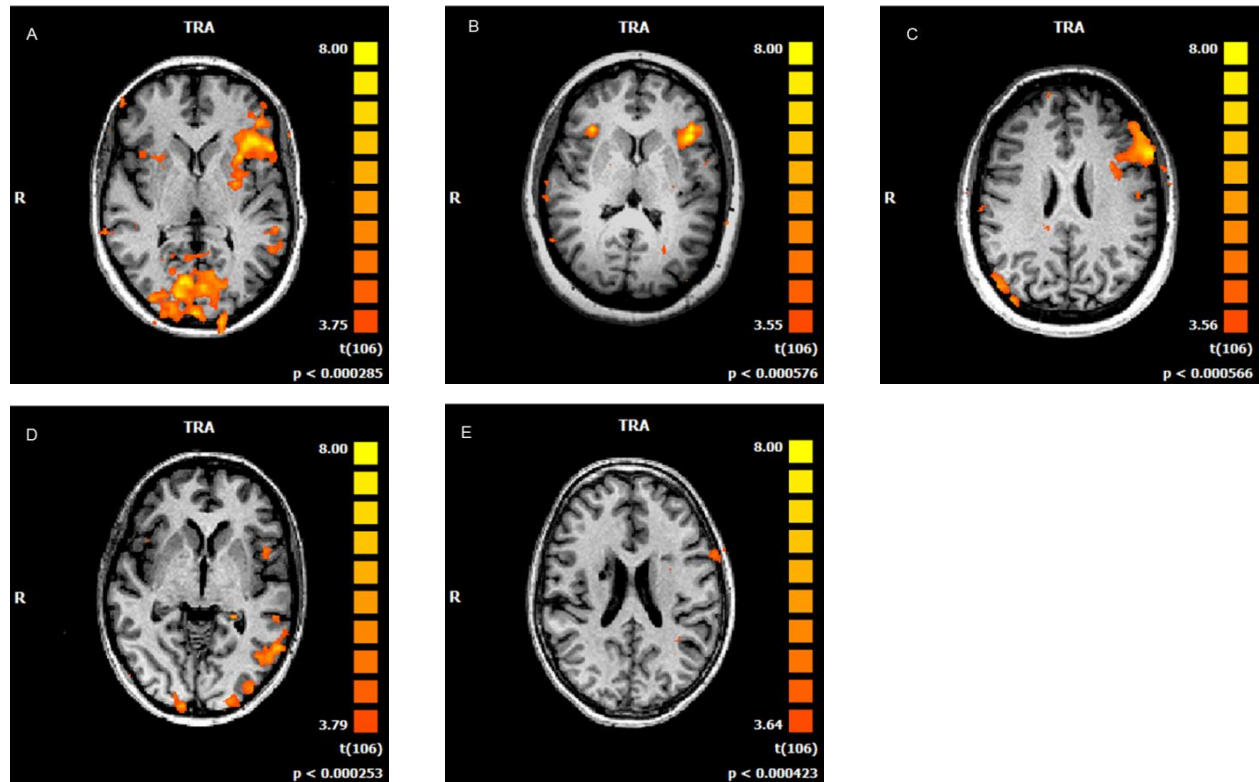


Figure 4. Language dominance shown for each control subject ($n = 3$) and for each UWD patient. During verb generation versus tones, left-hemisphere language was established in each subject. (A), control subject 1; (B), control subject 2; (C), control subject 3; (D), UWD patient 1; (E), UWD patient 2. The functional maps are displayed at $P < .001$, uncorrected, and are superimposed on each subject's native brain. R = right.

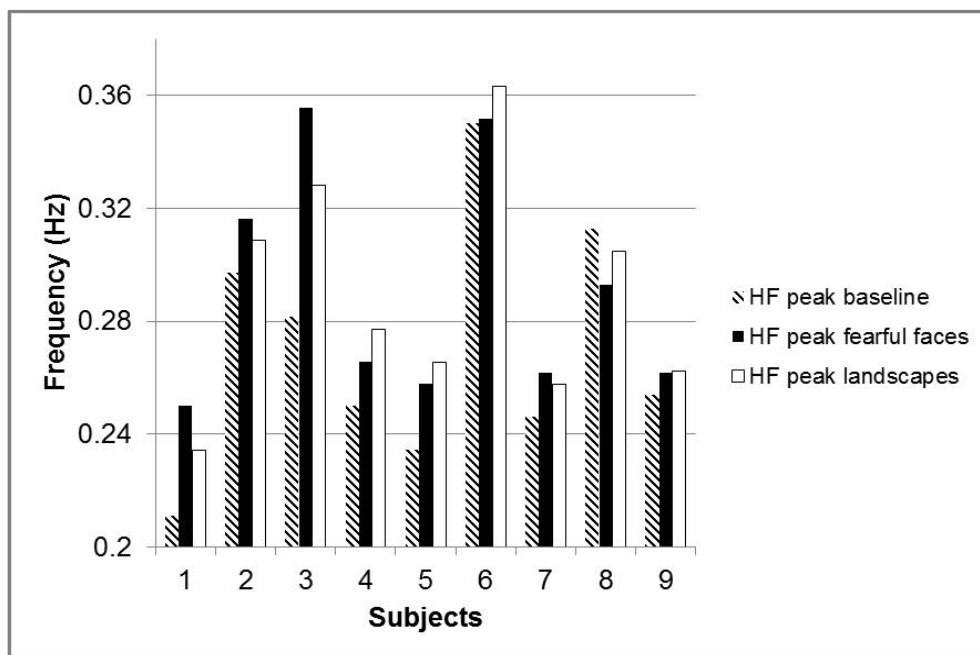


Figure 5. Heart rate variability (HRV) high (HF) frequency peak values for each control subject and for each UWD patient. The patterns of the HF peaks at rest, during the fearful face condition, and during the landscape condition do not fundamentally differ between the control subjects (subject 1-7), patient 1 (subject 8), and patient 2 (subject 9).

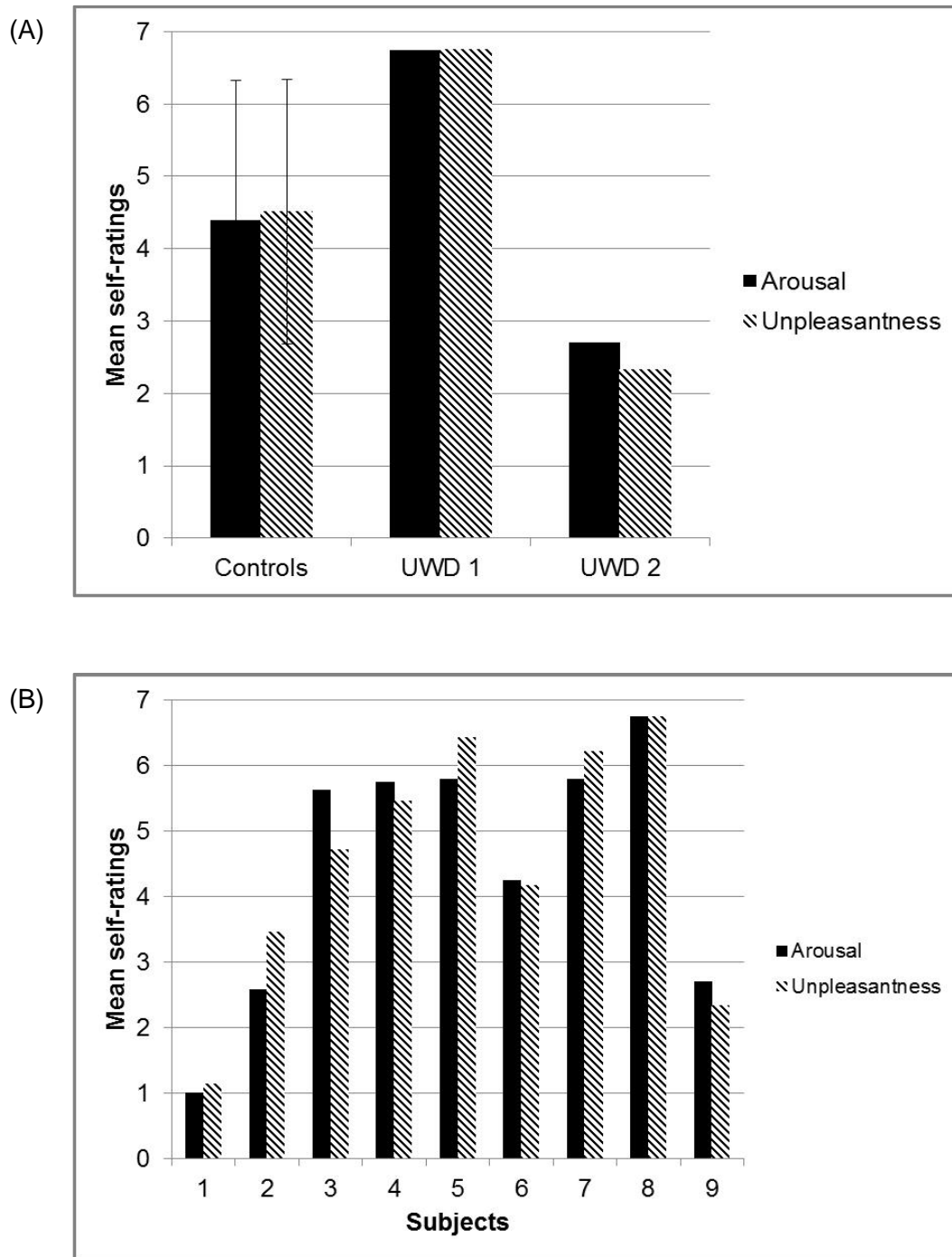


Figure 6. Mean ratings of arousal and unpleasantness in the controls and in each UWD patient. (A) Patient 1 experienced the fearful face scenes more arousing ($M = 6.75$) and more unpleasant ($M = 6.75$) than the control group ($n = 7$; $M_{\text{arousal}} = 4.40$, $SD_{\text{arousal}} = 1.92$; $M_{\text{unpleasantness}} = 4.50$, $SD_{\text{unpleasantness}} = 1.83$). By contrast, patient 2 perceived the fearful face scenes less arousing ($M = 2.71$) and less unpleasant ($M = 2.33$) than the control group ($n = 7$). (B) However, compared to each control subject's individual mean ratings (subjects 1-7), the mean arousal and unpleasantness ratings of each UWD patient (patient 1 = subject 8; patient 2 = subject 9) were not generally different.

References

- Adolphs, R., Damasio, H., Tranel, D., & Damasio, A. R. (1996). Cortical systems for the recognition of emotion in facial expressions. *The Journal of Neuroscience*, *16*, 7678-7687.
- Adolphs, R., Russell, J. A., & Tranel, D. (1999). A role for the human amygdala in recognizing emotional arousal from unpleasant stimuli. *Psychological Science*, *10*, 167-171.
- Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, *372*, 669-672.
- Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1995). Fear and the human amygdala. *The Journal of Neuroscience*, *15*, 5879-5891.
- Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., . . . Damasio, A. R. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, *37*, 1111-1117.
- Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., & Damasio, A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, *269*, 1115-1118.
- Becker, B., Mihov, Y., Scheele, D., Kendrick, K. M., Feinstein, J. S., Matusch, A., . . . Hurlemann, R. (2012). Fear processing and social networking in the absence of a functional amygdala. *Biological Psychiatry*, *72*, 70-77.
- Berntson, G. G., Bigger, J. T., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., . . . Stone, P. H. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology*, *34*, 623-648.
- Borod, J. C., Cicero, B. A., Obler, L. K., Welkowitz, J., Erhan, H. M., Santschi, C., . . . Whalen, J. R. (1998). Right hemisphere emotional perception: evidence across multiple channels. *Neuropsychology*, *12*, 446-458.
- Broicher, S. D., Frings, L., Huppertz, H. J., Grunwald, T., Kurthen, M., Kramer, G., & Jokeit, H. (2012). Alterations in functional connectivity of the amygdala in unilateral mesial temporal lobe epilepsy. *Journal of Neurology*, *259*, 2546-2554.
- Calder, A. J. (1996). Facial emotion recognition after bilateral amygdala damage: differentially severe impairment of fear. *Cognitive Neuropsychology*, *13*, 699-745.

- Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience & Biobehavioral Reviews*, 26, 321-352.
- Craig, A. D. (2005). Forebrain emotional asymmetry: a neuroanatomical basis? *Trends in Cognitive Sciences*, 9, 566-571.
- Critchley, H. D., Mathias, C. J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B. K., . . . Dolan, R. J. (2003). Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain*, 126, 2139-2152.
- Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, 15, 353-375.
- Feinstein, J. S., Adolphs, R., Damasio, A., & Tranel, D. (2011). The human amygdala and the induction and experience of fear. *Current Biology*, 21, 34-38.
- Feinstein, J. S., Buzza, C., Hurlemann, R., Follmer, R. L., Dahdaleh, N. S., Coryell, W. H., . . . Wemmie, J. A. (2013). Fear and panic in humans with bilateral amygdala damage. *Nature Neuroscience*, 16, 270-272.
- Friston, K. J., Ashburner, J. T., Kiebel, S. J., Nichols, T. E., & Penny, W. D. (2007). *Statistical parametric mapping: The analysis of functional brain images*. London: Academic Press.
- Goebel, R., Esposito, F., & Formisano, E. (2006). Analysis of functional image analysis contest (FIAC) data with Brainvoyager QX: from single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Human Brain Mapping*, 27, 392-401.
- Fourie, M. M., Rauch, H. G., Morgan, B. E., Ellis, G. F., Jordaan, E. R., & Thomas, K. G. (2011). Guilt and pride are heartfelt, but not equally so. *Psychophysiology*, 48, 888-899.
- Hirsch, J. A., & Bishop, B. (1981). Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. *American Journal of Physiology-Heart and Circulatory Physiology*, 241, 620-629.
- Ives-Deliperi, V. L., Butler, J. T., & Meintjes, E. M. (2013). Functional MRI language mapping in pre-surgical epilepsy patients: findings from a series of patients in the Epilepsy Unit at Mediclinic Constantiaberg. *South African Medical Journal*, 103, 363-368.

- Klumpers, F., Morgan, B., Terburg, D., Stein, D. J., & van Honk, J. (2014). Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdala damage. *Social Cognitive and Affective Neuroscience*. doi: 10.1093/scan/nsu164
- LeDoux, J. E. (1996). *The emotional brain*. New York: Simon and Schuster.
- Mihov, Y., Kendrick, K. M., Becker, B., Zschernack, J., Reich, H., Maier, W., . . . Hurlemann, R. (2013). Mirroring fear in the absence of a functional amygdala. *Biological Psychiatry*, 73, e9-e11.
- Montano, N., Porta, A., & Malliani, A. (2001). Evidence for central organization of cardiovascular rhythms. *Annals of the New York Academy of Sciences*, 940, 299-306.
- Öhman, A., & Mineka, S. (2001). Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological Review*, 108, 483-522.
- Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience*, 9, 148-158.
- Pessoa, L. (2010). Emotion and cognition and the amygdala: from “what is it?” to “what's to be done?”. *Neuropsychologia*, 48, 3416-3429.
- Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron*, 48, 175-187.
- Price, J. L. (1999). Prefrontal cortical networks related to visceral function and mood. *Annals of the New York Academy of Sciences*, 877, 383-396.
- Rahman, F., Pechnik, S., Gross, D., Sewell, L., & Goldstein, D. S. (2011). Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Clinical Autonomic Research*, 21, 133-141.
- Schacher, M., Haemmerle, B., Woermann, F. G., Okujava, M., Huber, D., Grunwald, T., . . . Jokeit, H. (2006). Amygdala fMRI lateralizes temporal lobe epilepsy. *Neurology*, 66, 81-87.
- Siebert, M., Markowitsch, H. J., & Bartel, P. (2003). Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. *Brain*, 126, 2627-2637.
- Terburg, D., Morgan, B. E., Montoya, E. R., Hooge, I. T., Thornton, H. B., Hariri, A. R., . . . van Honk, J. (2012). Hypervigilance for fear after basolateral amygdala damage in humans. *Translational Psychiatry*, 2, e115.

- Thornton, H. B., Nel, D., Thornton, D., van Honk, J., Baker, G. A., & Stein, D. J. (2008). The neuropsychiatry and neuropsychology of lipid proteinosis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 20, 86-92.
- Toller, G., Adhimoolam, B., Grunwald, T., Huppertz, H.-J., Kurthen, M., Rankin, K. P., & Jokeit, H. (2015). Right mesial temporal lobe epilepsy impairs empathy-related brain responses to dynamic fearful faces. *Journal of Neurology*. doi: 10.1007/s00415-014-7622-2
- Tranel, D., Gullickson, G., Koch, M., & Adolphs, R. (2006). Altered experience of emotion following bilateral amygdala damage. *Cognitive Neuropsychiatry*, 11, 219-232.

4 Summary and general discussion

Using behavioral, neuroimaging and psychophysiological measures, the overall objective of the present thesis was to investigate the impact of chronic unilateral mesial temporal lobe epilepsy (MTLE) and Urbach-Wiethe disease (UWD) on memory and social-cognitive processing.

The aim of the first publication was to investigate the diagnostic value of nonvisual spatial navigation fMRI to lateralize unilateral MTLE in an extraordinary patient with refractory left mesial temporal lobe epilepsy (LMTLE) and accompanying congenital blindness. This research question was based on previous evidence of cross-modal plasticity following congenital blindness that enables blind people to form spatial representations despite their lack of visual experience (Cattaneo et al., 2008; Struiksma, Noordzij, & Postma, 2009). To examine whether nonvisual spatial navigation could sufficiently activate mesial temporal lobe regions for individual memory lateralization, the patient was instructed to mentally navigate through a number of familiar routes by focusing on nonvisual sensory and linguistic cues. Our results showed the diagnostic value of nonvisual spatial navigation to lateralize MTLE in a congenitally blind patient. These findings indicate that the paradigm could help clinicians assess the risk of postsurgical amnesia in congenitally blind patients with unilateral MTLE, who are particularly reliant on intact memory.

The second publication intended to examine whether unilateral MTLE was associated with altered empathy-related brain responses in the amygdala, PAG, and AI during the observation of dynamic fearful faces. This question was derived from previous evidence of partly shared neuronal representations for self- and other-related feeling states, including anger, sadness, and fear (Wicker et al., 2003; de Gelder, Snyder, Greve, Gerard, & Hadjikhani, 2004; de Greck et al., 2012). To examine whether unilateral MTLE was specifically associated with reduced empathy-related brain responses to dynamic fearful faces and to control for potential attenuation of BOLD activity caused by antiepileptic and antidepressant medication, an epilepsy control group consisting of patients with extra-mesial temporal lesions and seizure onsets (extra-MTLE) was included. The main finding was that right mesial temporal lobe epilepsy (RMTLE) was associated with decreased activity predominantly in the right amygdala and also in the bilateral PAG but normal activity in the right AI. The results of the extra-MTLE group demonstrated that these reduced amygdala and PAG responses were not merely an effect of antiepileptic and

antidepressant medication. Combined with the decreased empathic concern found in the RMTLE group, this study provides neurobehavioral evidence that patients with RMTLE are at increased risk for reduced empathy towards others' internal states.

The objective of the third publication was to study the relationship between self-reported affective and cognitive empathy and gray matter volume in unilateral MTLE. This research question was derived from previous evidence showing that MTLE is associated with brain atrophy in temporal, frontal, and parietal regions that are critical for affective and cognitive empathy (Keller & Roberts, 2008; Bonilha et al., 2010). In addition, the question was based on the diminished self-reported empathy and the decreased empathy-related brain responses to dynamic fearful faces we found in the RMTLE group in particular. Consistent with these fMRI results, both lower affective and cognitive empathy was associated with smaller volume in predominantly right fronto-limbic regions, including the right mesial temporal lobe, and in the bilateral midbrain. The only region that was associated with both affective and cognitive empathy was the right mesial temporal lobe. In line with the reduced empathy-related brain responses in the right amygdala and the bilateral PAG of the RMTLE group, these findings suggest that volume loss in right fronto-limbic regions, including the right mesial temporal lobe, and in the bilateral midbrain contributes to the etiopathogenesis of reduced empathy in unilateral MTLE.

The fourth publication was aimed at investigating the impact of incomplete bilateral amygdala damage in two UWD patients on the functioning of unaffected amygdala regions. This research question was based on previous findings showing increased amygdala responses to subconsciously presented fearful faces in a group of five UWD patients with incomplete amygdala damage (Terburg et al., 2012). Because of the high interindividual variability in fear-related impairments in the entire population of UWD, the dynamic fearful face task we administered was one that had previously been shown to activate the bilateral amygdala in healthy individuals (Schacher, Haemmerle, et al., 2006). In addition, the patients' changes in heart rate variability (HRV) and their subjective arousal were assessed during the observation of the faces outside the scanner. These measurements were included because of the top-down control of the amygdala on autonomic brainstem regions and based on our finding of bilateral PAG responses to the dynamic fearful faces in the group of healthy Caucasians. In contrast to

each control subject, neither patient demonstrated activity in the unaffected amygdala regions. Despite interindividual differences, neither patient's individual patterns of autonomic and subjective arousal to the faces generally differed from the control group. These preliminary findings indicate that the two UWD patients showed bilateral amygdala dysfunction with at least partly preserved physiological and subjective arousal in response to the dynamic fearful faces.

4.1 Theoretical implications

The finding that nonvisual spatial navigation was an appropriate task to lateralize late-onset LMTLE in a patient with congenital blindness is in support of early evidence from patients with mesial temporal lobe lesions showing that anterograde amnesia affects both visual and nonvisual modalities (Milner, 1972; Squire et al., 2001). Moreover, this result is consistent with the ability of congenitally blind people to form spatial episodic memories despite their lack of visual memory, which is based on adaptive functional reorganization of brain regions mediating the nonvisual sensory and verbal modalities (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Kupers et al., 2006). In the presence of left hemisphere language dominance, the patient showed subjective and neuropsychologically measured episodic memory impairments, which demonstrates the typical impact of left mesial temporal lobe damage due to chronic MTLE on verbal episodic memory (Helmstaedter et al., 1997; Hermann et al., 1997).

The present work demonstrated a high association between the right amygdala and the processing of dynamic fearful faces in different groups, including healthy Caucasians, patients with LMTLE, and patients with extra-MTLE. Based on previous evidence showing that the paradigm is associated with bilateral amygdala activity in healthy individuals (Schacher, Haemmerle, et al., 2006), the task was applied for the first time to three healthy women of mixed ancestry. Consistent with the group results of the healthy Caucasians and the patients with LMTLE and extra-MTLE, each of the three women demonstrated stronger activity in the right than in the left amygdala. When considered together with the right-lateralized activity in the AI found in the healthy control, LMTLE, and RMTLE groups during the observation of the fearful faces, these converging findings can be well integrated into Craig's (2005) recent homeostatic neuroanatomical model of emotional asymmetry. Accordingly, the right AI is

associated predominantly with sympathetic activity, and thus with arousal and negative affect, and the left AI is mainly related to parasympathetic activity, and thus to nourishment and to positive affect (Craig, 2005). Combined with the lack of amygdala activity found in the RMTLE group and in the two UWD cases during the processing of the faces, the current thesis provides concurrent evidence for the crucial role of the right amygdala for empathic feelings of fear.

Moreover, the current findings demonstrated that the dynamic fearful face task was associated with activity in the bilateral PAG in the healthy Caucasian group, which is highly consistent with the involvement of the PAG in autonomic fear responses in the self (LeDoux, 1996) and with the crucial role of internal bodily states for firsthand and empathic feeling states (Craig, 2009; Singer et al., 2009). In line with the reciprocal connections between the amygdala and the PAG (Davis, 1992; Price, 1999; Cardinal et al., 2002), our findings demonstrated for the first time that RMTLE in particular was specifically associated with decreased PAG responses to dynamic fearful faces. Although such decreased PAG responses to salient emotional stimuli are likely to reflect decreased autonomic arousal, this question remains open as the present work did not incorporate psychophysiological measures in the epilepsy groups. The decreased empathy-related activity in the right amygdala and the bilateral PAG shown in the RMTLE group is in line with the finding that lower affective and cognitive empathy in unilateral MTLE was related to smaller volume in right fronto-limbic regions, including the right mesial temporal lobe, and the bilateral midbrain. The important role of the right mesial temporal lobe for empathy was further supported by the finding that higher empathy reported across the control, RMTLE, and LMTLE groups was associated with increased right amygdala responses to fearful faces.

Overall, these converging neurobehavioral findings indicate that patients with RMTLE are at increased risk for reduced affective and cognitive empathy towards others' internal states. Due to the complex etiopathogenesis of impaired social cognition in chronic MTLE (Figure 2, p. 16), the influence of comorbid depression, AEDs, age at epilepsy onset, and duration and chronicity (extra-MTLE group) of epilepsy was controlled for in our studies. Consequently, the neurobehavioral findings clearly suggest that structural and functional changes in the right mesial temporal lobe as well as in anatomically remote right fronto-limbic and bilateral brainstem regions are an important cause of diminished empathy in chronic unilateral MTLE.

These results confirm previous evidence showing that early-onset bilateral and right MTLE in particular are specifically associated with deficits in the recognition and neuronal processing of negative facial expressions (e.g., Meletti et al., 2003; Benuzzi et al., 2004; Meletti et al., 2009; Labudda et al., 2013). Specifically, our findings indicate that brain abnormalities in the right mesial temporal lobe and its brainstem connections are a major cause of impaired social cognition in unilateral MTLE. These results confirm recent models that highlight the importance of interoceptive information from the body for both self- and other-related affective states (Craig, 2009; Singer et al., 2009). Overall, the present work suggests that functional and structural brain changes in the epileptogenic mesial temporal lobe as well as in anatomically remote brain regions significantly contribute to social-cognitive impairments in chronic MTLE. This conclusion is in line with previous evidence showing that the cognitive profiles of MTLE patients are significantly determined by brain abnormalities within and outside the epileptogenic mesial temporal lobes (e.g., Jokeit, Seitz, et al., 1997; Jokeit & Ebner, 1999; Elger et al., 2004).

Consistent with the proposed role of the right AI for the subjective awareness of both self- and other-related negative emotions (Craig, 2005, 2009; Singer et al., 2009), right-lateralized AI activation was found in the healthy Caucasian group as well as in the LMTLE and RMTLE groups during the processing of dynamic fearful faces. The finding of right AI activation in the RMTLE patients is remarkable considering their widespread pattern of hypoactivation and the functional connections between the right amygdala and the right AI (Seeley et al., 2007; Tomasi & Volkow, 2011). In conjunction with the finding of thalamic activity observed only in the RMTLE group, these results suggest that the RMTLE patients recruited a thalamo-insular pathway (Seeley et al., 2007) that may reflect either a compensatory or a disinhibitory effect associated with the right mesial temporal lobe lesion. These findings indicate that the cortical representation and integration of interoceptive information involved in vicarious experiences of fear was unaffected by both right and left MTLE. This result is congruent with our preliminary data from the two UWD cases showing that the patients reported at least partly preserved subjective arousal despite their bilateral amygdala dysfunction in response to dynamic fearful faces. As the right AI, the thalamus, the amygdala, and the PAG are part of the intrinsic “salience network” (Seeley et al., 2007), future resting-state studies should investigate these regions’

intrinsic connectivity patterns in both unilateral MTLE and UWD. Such studies would give important and complementary insights into the impact of right and bilateral mesial temporal lobe damage on the connectivity between the right amygdala and the right AI.

The preliminary findings from the two UWD cases indicated that their bilateral amygdala dysfunction was associated with at least partly preserved patterns of autonomic and subjectively perceived arousal. In light of the strong hypoactivation shown in the RMTLE group that included the bilateral amygdala and the bilateral PAG, the result of bilateral amygdala dysfunction with preserved autonomic and subjective arousal in the two UWD patients may seem contradictory. Based on the selective and incomplete amygdala damage in the two UWD cases, one likely reason for their preserved arousal is that cortical regions such as the anterior cingulate cortex and possibly also unaffected parts of the amygdala (LeDoux, 1996; Cardinal et al., 2002; Critchley et al., 2003) may be sufficient to activate brainstem regions that generate the physiological responses to fear-related stimuli. Another factor that may explain the presence of autonomic and subjectively perceived arousal despite the bilateral amygdala dysfunction is that the two UWD cases did not suffer from widespread brain pathology as in the occurrence of comorbid MTLE. Consequently, their brain damage and the resulting neuronal and cognitive dysfunctions were predominantly restricted to the bilateral amygdala and were not additionally affected by epilepsy-related factors including recurrent seizures, interictal epileptic discharges, and AEDs (Elger et al., 2004). This conclusion is corroborated by the finding that the RMTLE group and the two UWD patients differed in their patterns of extra-amygdalar activity during fearful face processing. While RMTLE was associated with a widespread pattern of hypoactivation within and outside the mesial temporal lobes, each UWD patient's pattern of extra-amygdalar activity was similar to that found in the control subjects. Although group and single case results are not directly comparable, they nevertheless suggest that the negative impact of RMTLE in particular on social-cognitive processing is more pronounced than that of selective and incomplete bilateral amygdala damage due to UWD without comorbid epilepsy. This conclusion is consistent with previous evidence showing impaired prosodic emotion recognition in MTLE (Bonora et al., 2011; Broicher, Kuchukhidze, et al., 2012; Meletti et al., 2014) but preserved prosodic emotion recognition in UWD (Adolphs & Tranel, 1999; Bach et al., 2013; Meletti et al., 2014). These previous and current findings suggest that the more extensive

brain damage found in MTLE compared to UWD may result in more pronounced social-cognitive deficits. As the individual patterns of autonomic and subjectively perceived arousal differed between the two UWD patients, the present neurobehavioral and psychophysiological findings also support previous evidence that UWD is associated with an interindividually varying endophenotype. Consequently, UWD cannot be considered a uniform model of amygdala lesion and dysfunction, which in turn limits the generalization of previous and the present study findings to the entire UWD population.

Overall, the converging neuroimaging and psychophysiological findings from healthy subjects of different ethnicity and from patients with epilepsy and UWD highlight the dual role of the amygdala for salience processing and for the coordination of appropriate physiological responses; consequently, they support the view of the amygdala as the “controller of the brainstem” (Cardinal et al., 2002). Moreover, these results are consistent with early theories of emotion (James, 1884; Lange, 1885) and current models of human awareness (Craig, 2009) and empathy (Singer et al., 2009), suggesting that interoceptive information from the body is essential for both self-related and empathic feeling states. Therefore, to obtain a detailed picture of the etiopathogenesis and nature of impaired social cognition in epilepsy, UWD, and other brain disorders, future research is encouraged to put greater emphasis on subcortical regions that process interoceptive information from the body.

4.2 Clinical implications

To date, the diagnostic value of visual-spatial navigation fMRI to lateralize unilateral MTLE has been demonstrated across a broad spectrum of sighted patients, including children, the elderly, and individuals with mental handicaps (Jokeit et al., 2001). The present work showed that nonvisual spatial navigation fMRI was also an appropriate task to lateralize LMTLE in a patient with congenital blindness. As LMTLE is associated in particular with a high risk for postsurgical decline in verbal episodic memory (Helmstaedter, Brosch, et al., 2004; Janszky et al., 2005), the present findings may provide clinicians with important information for the clinical diagnostics and therapy of blind patients with chronic MTLE, who are especially reliant on intact memory. However, to confirm and validate the diagnostic value of the task, further patients

with unilateral MTLE and concurrent (congenital) blindness need to be studied pre- and postoperatively.

The present thesis extends previous findings on emotion recognition and ToM suggesting that RMTLE in particular is a specific risk factor for diminished empathy towards others' internal states. Reduced empathy has a highly negative impact on social interactions and social relationships and likely contributes to the psychosocial maladjustment frequently associated with epilepsy that lead to unemployment and lower marriage rates (Strine et al., 2005; Kobau et al., 2007). Based on the finding that brain changes in the mesial temporal lobe and the brainstem were related to impaired social cognition in chronic MTLE, altered emotional and psychophysiological responses to salient social stimuli are likely to affect the social interactions and prosocial behavior of affected patients. This conclusion is in line with early and more recent models suggesting that the re-mapping of interoceptive information from the body may allow the brain to judge and predict the effects of stimuli that are homeostatically relevant to the organism (Damasio, Everitt, & Bishop, 1996; Craig, 2009; Singer et al., 2009).

Overall, the present thesis sheds more light on the early neuropsychiatric concept of Waxman and Geschwind (1975) who considered specific interictal behavioral changes of MTLE patients as manifestations of fronto-limbic lesions. Although previous and the current findings suggest that social-cognitive deficits in MTLE are less pronounced than historically described by Waxman and Geschwind (1975), they confirm the authors' early notion that the underlying brain pathology is a major cause of social-cognitive impairments in chronic MTLE.

4.3 Limitations, open questions, and outlook

In the present work, psychophysiological measures were not applied to the epilepsy groups during fearful face processing. Consequently, it remains unanswered whether the reduced amygdala and PAG responses in the MTLE groups were accompanied by reduced autonomic arousal in response to the faces. Future research could investigate the direct association between reduced PAG and autonomic responses in chronic MTLE by simultaneous fMRI and psychophysiological recordings during fearful face processing. The additional use of eye-tracking would help to exclude the possibility that the reduced empathy-related brain responses in the MTLE patients resulted from an atypical visual exploration of the faces. This combined use of

fMRI, psychophysiological measures, and eye-tracking during the processing of the dynamic fearful faces is also proposed for studies in UWD patients, which would provide comprehensive complementary information on the impact of selective bilateral mesial temporal lobe damage on fearful face processing. In a further step, one could examine the influence of comorbid epilepsy in UWD on the neuroimaging and psychophysiological measures by comparing UWD patients with and without comorbid MTLE.

Despite previous evidence showing that early-onset MTLE is associated with an increased severity of social-cognitive impairments (e.g., Meletti et al., 2003; Shaw et al., 2004; Meletti et al., 2009; Giovagnoli et al., 2011), due to small sample sizes the present work did not specifically examine the effect of early-onset vs. late-onset of MTLE on the processing of fearful faces. Nevertheless, the asymmetric impact of right and left MTLE on both empathy-related brain regions and self-reported empathy cannot be attributed to differences in age at epilepsy onset, because the LMTLE and RMTLE groups were matched with regard to this variable.

Based on the current findings of reduced empathy-related brain responses in presurgical patients with chronic unilateral MTLE, the question arises of how the dynamic fearful faces would be processed after successful mesial temporal lobe resection. This open question is particularly interesting in light of recent longitudinal evidence suggesting that emotion recognition and also ToM abilities generally remain stable before and one year after epilepsy surgery (Shaw et al., 2007; Amlerova et al., 2014). Consistent with growing evidence on the recovery of memory and language functions in seizure-free postsurgical MTLE patients (Helmstaedter et al., 2003; Bonelli et al., 2012), preliminary longitudinal findings on fearful face processing show adaptive functional reorganization and superior emotion recognition abilities in two postsurgical RMTLE patients (Benuzzi et al., 2014).

In the current work, behavioral aspects of empathy were assessed only by self-reports. Although a psychometrically well-validated empathy questionnaire was used (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Rankin et al., 2006; Banissy, Kanai, Walsh, & Rees, 2012), we cannot exclude the possibility that the self-ratings of the healthy controls and the MTLE patients were biased either by socially desirable responding or by poor insight especially associated with the right hemisphere lesion of the RMTLE group. Consequently, future studies on empathy in MTLE are encouraged to include both self and informant ratings.

Finally, because hippocampal sclerosis (HS) is the most common neuropathological substrate of MTLE, only presurgical MTLE patients with HS were included in the present group studies. This methodological approach was chosen in order to obtain data that are generalizable to a large proportion of MTLE patients. However, the generalization of the present results to other etiologies of MTLE, including tumors, dysplasias, and cavernomas may be limited, because they are usually less restricted to a particular structure than HS and can highly vary with regard to the extent of the corresponding lesion.

In summary, the present work showed that both chronic MTLE and UWD affect memory and social-cognitive functions that rely on structures within and outside the mesial temporal lobes. Our converging neurobehavioral and psychophysiological findings from patients with chronic unilateral MTLE and UWD highlight the crucial role of right fronto-limbic and bilateral brainstem regions for normal social cognition. In particular, the present work contributes to the current literature by emphasizing that amygdala-brainstem dysfunctions constitute a major cause of impaired social cognition in MTLE and UWD. Moreover, this work provides new clinical findings that may help clinicians in terms of diagnosis and therapy of rare patients with chronic MTLE. In this way, the present thesis contributes to our theoretical and clinical understanding of cognitive comorbidities in MTLE and UWD, and provides new lesion data on certain functions of the mesial temporal lobes and its connections.

5 References

- Abu-Akel, A., & Shamay-Tsoory, S. (2011). Neuroanatomical and neurochemical bases of theory of mind. *Neuropsychologia*, 49, 2971-2984.
- Adolphs, R. (2001). The neurobiology of social cognition. *Current Opinion in Neurobiology*, 11, 231-239.
- Adolphs, R. (2009). The social brain: neural basis of social knowledge. *Annual Review of Psychology*, 60, 693.
- Adolphs, R. (2010). What does the amygdala contribute to social cognition? *Annals of the New York Academy of Sciences*, 1191, 42-61.
- Adolphs, R., Cahill, L., Schul, R., & Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learning & Memory*, 4, 291-300.
- Adolphs, R., Damasio, H., Tranel, D., & Damasio, A. R. (1996). Cortical systems for the recognition of emotion in facial expressions. *The Journal of Neuroscience*, 16, 7678-7687.
- Adolphs, R., Russell, J. A., & Tranel, D. (1999). A role for the human amygdala in recognizing emotional arousal from unpleasant stimuli. *Psychological Science*, 10, 167-171.
- Adolphs, R., & Tranel, D. (1999). Intact recognition of emotional prosody following amygdala damage. *Neuropsychologia*, 37, 1285-1292.
- Adolphs, R., & Tranel, D. (2000). Emotion recognition and the human amygdala. In Aggleton J. P. (editor), *The amygdala: A functional analysis* (p. 587-630). New York: Oxford University Press.
- Adolphs, R., Tranel, D., & Damasio, A. R. (1998). The human amygdala in social judgment. *Nature*, 393, 470-474.
- Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, 372, 669-672.
- Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1995). Fear and the human amygdala. *The Journal of Neuroscience*, 15, 5879-5891.

- Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., . . . Damasio, A. R. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, 37, 1111-1117.
- Aggleton, J., & Saunders, R. (2000). The Amygdala—what's happened in the last decade? In Aggleton J. P. (editor), *The Amygdala: A Functional Analysis* (p. 1-30). Oxford University Press: Oxford.
- Alessio, A., Damasceno, B. P., Camargo, C. H. P., Kobayashi, E., Guerreiro, C. A. M., & Cendes, F. (2004). Differences in memory performance and other clinical characteristics in patients with mesial temporal lobe epilepsy with and without hippocampal atrophy. *Epilepsy & Behavior*, 5, 22-27.
- Amedi, A., Raz, N., Pianka, P., Malach, R., & Zohary, E. (2003). Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. *Nature Neuroscience*, 6, 758-766.
- Amlerova, J., Cavanna, A. E., Bradac, O., Javurkova, A., Raudenska, J., & Marusic, P. (2014). Emotion recognition and social cognition in temporal lobe epilepsy and the effect of epilepsy surgery. *Epilepsy & Behavior*, 36, 86-89.
- Appenzeller, S., Chaloult, E., Velho, P., Macedo de Souza, E., Zanardi Araújo, V., Cendes, F., & Li, L. M. (2006). Amygdalae calcifications associated with disease duration in lipid proteinosis. *Journal of Neuroimaging*, 16, 154-156.
- Arnold, S., Schlaug, G., Niemann, H., Ebner, A., Luders, H., Witte, O., & Seitz, R. (1996). Topography of interictal glucose hypometabolism in unilateral mesiotemporal epilepsy. *Neurology*, 46, 1422-1422.
- Avila, C., Barros-Loscertales, A., Forn, C., Mallo, R., Parcet, M. A., Belloch, V., . . . Gonzalez-Darder, J. M. (2006). Memory lateralization with 2 functional MR imaging tasks in patients with lesions in the temporal lobe. *AJNR American Journal of Neuroradiology*, 27, 498-503.
- Bach, D. R., Hurlemann, R., & Dolan, R. J. (2013). Unimpaired discrimination of fearful prosody after amygdala lesion. *Neuropsychologia*, 51, 2070-2074.
- Bancaud, J., Henriksen, O., Rubio-Donnadieu, F., Seino, M., Dreifuss, F., & Penry, J. (1981). Commission on classification and terminology of the international league against epilepsy.

- Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*, 22, 489-501.
- Banissy, M. J., Kanai, R., Walsh, V., & Rees, G. (2012). Inter-individual differences in empathy are reflected in human brain structure. *Neuroimage*, 62, 2034-2039.
- Batut, A. C., Gounot, D., Namer, I. J., Hirsch, E., Kehrli, P., & Metz-Lutz, M. N. (2006). Neural responses associated with positive and negative emotion processing in patients with left versus right temporal lobe epilepsy. *Epilepsy & Behavior*, 9, 415-423.
- Bear, D. M., & Fedio, P. (1977). Quantitative analysis of interictal behavior in temporal lobe epilepsy. *Archives of Neurology*, 34, 454-467.
- Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., & Damasio, A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, 269, 1115-1118.
- Becker, B., Mihov, Y., Scheele, D., Kendrick, K. M., Feinstein, J. S., Matusch, A., . . . Hurlemann, R. (2012). Fear processing and social networking in the absence of a functional amygdala. *Biological Psychiatry*, 72, 70-77.
- Benuzzi, F., Meletti, S., Zamboni, G., Calandra-Buonaura, G., Serafini, M., Lui, F., . . . Nichelli, P. (2004). Impaired fear processing in right mesial temporal sclerosis: a fMRI study. *Brain Research Bulletin*, 63, 269-281.
- Benuzzi, F., Zamboni, G., Meletti, S., Serafini, M., Lui, F., Baraldi, P., . . . Nichelli, P. F. (2014). Recovery from emotion recognition impairment after temporal lobectomy. *Frontiers in Neurology*, 5, 1-8.
- Bernhardt, B. C., & Singer, T. (2012). The neural basis of empathy. *Annual Review of Neuroscience*, 35, 1-23.
- Bickart, K. C., Hollenbeck, M. C., Barrett, L. F., & Dickerson, B. C. (2012). Intrinsic amygdala–cortical functional connectivity predicts social network size in humans. *The Journal of Neuroscience*, 32, 14729-14741.
- Bonelli, S. B., Powell, R., Yogarajah, M., Thompson, P. J., Symms, M. R., Koepp, M. J., & Duncan, J. S. (2009). Preoperative amygdala fMRI in temporal lobe epilepsy. *Epilepsia*, 50, 217-227.

- Bonelli, S. B., Thompson, P. J., Yogarajah, M., Vollmar, C., Powell, R. H. W., Symms, M. R., . . . Duncan, J. S. (2012). Imaging language networks before and after anterior temporal lobe resection: results of a longitudinal fMRI study. *Epilepsia*, *53*, 639-650.
- Bonilha, L., Edwards, J. C., Kinsman, S. L., Morgan, P. S., Fridriksson, J., Rorden, C., . . . Halford, J. J. (2010). Extrahippocampal gray matter loss and hippocampal deafferentation in patients with temporal lobe epilepsy. *Epilepsia*, *51*, 519-528.
- Bonilha, L., Rorden, C., Castellano, G., Cendes, F., & Li, L. M. (2005). Voxel-based morphometry of the thalamus in patients with refractory medial temporal lobe epilepsy. *Neuroimage*, *25*, 1016-1021.
- Bonora, A., Benuzzi, F., Monti, G., Mirandola, L., Pugnaghi, M., Nichelli, P., & Meletti, S. (2011). Recognition of emotions from faces and voices in medial temporal lobe epilepsy. *Epilepsy & Behavior*, *20*, 648-654.
- Borod, J. C., Cicero, B. A., Obler, L. K., Welkowitz, J., Erhan, H. M., Santschi, C., . . . Whalen, J. R. (1998). Right hemisphere emotional perception: evidence across multiple channels. *Neuropsychology*, *12*, 446-458.
- Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., . . . Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*, *17*, 875-887.
- Broicher, S. D., Frings, L., Huppertz, H. J., Grunwald, T., Kurthen, M., Kramer, G., & Jokeit, H. (2012). Alterations in functional connectivity of the amygdala in unilateral mesial temporal lobe epilepsy. *Journal of Neurology*, *259*, 2546-2554.
- Broicher, S. D., Kuchukhidze, G., Grunwald, T., Kramer, G., Kurthen, M., & Jokeit, H. (2012). "Tell me how do I feel"--emotion recognition and theory of mind in symptomatic mesial temporal lobe epilepsy. *Neuropsychologia*, *50*, 118-128.
- Broicher, S., Kuchukhidze, G., Grunwald, T., Kramer, G., Kurthen, M., Trinka, E., & Jokeit, H. (2010). Association between structural abnormalities and fMRI response in the amygdala in patients with temporal lobe epilepsy. *Seizure*, *19*, 426-431.
- Cahill, L., Prins, B., Weber, M., & McGaugh, J. L. (1994). β -Adrenergic activation and memory for emotional events. *Nature*, *371*, 702-704.

- Calder, A. J. (1996). Facial emotion recognition after bilateral amygdala damage: differentially severe impairment of fear. *Cognitive Neuropsychology*, 13, 699-745.
- Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience & Biobehavioral Reviews*, 26, 321-352.
- Carrington, S. J., & Bailey, A. J. (2009). Are there theory of mind regions in the brain? A review of the neuroimaging literature. *Human Brain Mapping*, 30, 2313-2335.
- Cattaneo, Z., Vecchi, T., Cornoldi, C., Mammarella, I., Bonino, D., Ricciardi, E., & Pietrini, P. (2008). Imagery and spatial processes in blindness and visual impairment. *Neuroscience and Biobehavioral Reviews*, 32, 1346-1360.
- Clusmann, H., Schramm, J., Kral, T., Helmstaedter, C., Ostertun, B., Fimmers, R., . . . Elger, C. E. (2002). Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. *Journal of Neurosurgery*, 97, 1131-1141.
- Cohn, M., St-Laurent, M., Barnett, A., & McAndrews, M. P. (2014). Social inference deficits in temporal lobe epilepsy and lobectomy: risk factors and neural substrates. *Social Cognitive and Affective Neuroscience*. doi: 10.1093/scan/nsu101
- Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in HM. *Seminars in Neurology*, 4, 249-259.
- Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*, 3, 655-666.
- Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology*, 13, 500-505.
- Craig, A. D. (2005). Forebrain emotional asymmetry: a neuroanatomical basis? *Trends in Cognitive Sciences*, 9, 566-571.
- Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, 10, 59-70.
- Critchley, H. D., Mathias, C. J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B. K., . . . Dolan, R. J. (2003). Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain*, 126, 2139-2152.

- Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, 7, 189-195.
- Damasio, A. R., Everitt, B., & Bishop, D. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex [and discussion]. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 351, 1413-1420.
- Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, 15, 353-375.
- Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Molecular Psychiatry*, 6, 13-34.
- de Gelder, B., Snyder, J., Greve, D., Gerard, G., & Hadjikhani, N. (2004). Fear fosters flight: a mechanism for fear contagion when perceiving emotion expressed by a whole body. *Proceedings of the National Academy of Sciences of the United States of America*, 101, 16701-16706.
- de Greck, M., Wang, G., Yang, X., Wang, X., Northoff, G., & Han, S. (2012). Neural substrates underlying intentional empathy. *Social Cognitive and Affective Neuroscience*, 7, 135-144.
- Desmet, S., Devos, S. A., Chan, I., Hamada, T., Dhooge, I., McGrath, J. A., & Naeyaert, J. M. (2005). Clinical and molecular abnormalities in lipoid proteinosis. *European Journal of Dermatology*, 15, 344-346.
- Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron*, 42, 855-863.
- Elger, C. E., Helmstaedter, C., & Kurthen, M. (2004). Chronic epilepsy and cognition. *The Lancet Neurology*, 3, 663-672.
- Emerson, R. G., Turner, C. A., Pedley, T. A., Walczak, T. S., & Forgione, M. (1995). Propagation patterns of temporal spikes. *Electroencephalography and Clinical Neurophysiology*, 94, 338-348.
- Engel, J. (1996). Introduction to temporal lobe epilepsy. *Epilepsy Research*, 26, 141-150.
- Feinstein, J. S., Adolphs, R., Damasio, A., & Tranel, D. (2011). The human amygdala and the induction and experience of fear. *Current Biology*, 21, 34-38.

- Feinstein, J. S., Buzza, C., Hurlemann, R., Follmer, R. L., Dahdaleh, N. S., Coryell, W. H., . . . Wemmie, J. A. (2013). Fear and panic in humans with bilateral amygdala damage. *Nature Neuroscience*, *16*, 270-272.
- Focke, N. K., Yogarajah, M., Bonelli, S. B., Bartlett, P. A., Symms, M. R., & Duncan, J. S. (2008). Voxel-based diffusion tensor imaging in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. *Neuroimage*, *40*, 728-737.
- Fraser, R. (1993). Psychosocial rehabilitation: a pre-and postoperative perspective. In Engel J. (editor), *Surgical Treatment of the Epilepsies* (p. 669-677). New York: Raven Press.
- Frith, U., & Frith, C. D. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences*, *358*, 459-473.
- Frith, C. D., & Frith, U. (2006). The neural basis of mentalizing. *Neuron*, *50*, 531-534.
- Gallagher, H. L., & Frith, C. D. (2003). Functional imaging of 'theory of mind'. *Trends in Cognitive Sciences*, *7*, 77-83.
- Giovagnoli, A. R., Franceschetti, S., Reati, F., Parente, A., Maccagnano, C., Villani, F., & Spreafico, R. (2011). Theory of mind in frontal and temporal lobe epilepsy: cognitive and neural aspects. *Epilepsia*, *52*, 1995-2002.
- Giovagnoli, A. R., Parente, A., Villani, F., Franceschetti, S., & Spreafico, R. (2013). Theory of mind and epilepsy: what clinical implications? *Epilepsia*, *54*, 1639-1646.
- Gleissner, U., Helmstaedter, C., Schramm, J., & Elger, C. E. (2004). Memory outcome after selective amygdalohippocampectomy in patients with temporal lobe epilepsy: one-year follow-up. *Epilepsia*, *45*, 960-962.
- Grady, C. L., McIntosh, A. R., Rajah, M. N., Beig, S., & Craik, F. I. (1999). The effects of age on the neural correlates of episodic encoding. *Cerebral Cortex*, *9*, 805-814.
- Gu, X., Gao, Z., Wang, X., Liu, X., Knight, R. T., Hof, P. R., & Fan, J. (2012). Anterior insular cortex is necessary for empathetic pain perception. *Brain*, *135*, 2726-2735.
- Guimera, R., & Amaral, L. A. N. (2005). Functional cartography of complex metabolic networks. *Nature*, *433*, 895-900.
- Hamada, T., McLean, W. H., Ramsay, M., Ashton, G. H., Nanda, A., Jenkins, T., . . . McGrath, J. A. (2002). Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (ECM1). *Human Molecular Genetics*, *11*, 833-840.

- Helliwell, J. F., & Putnam, R. D. (2004). The social context of well-being. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 359, 1435-1446.
- Helmstaedter, C. (1999). Sex differences in material-specific cognitive functions related to language dominance: an intracarotid amobarbital study in left temporal lobe epilepsy. *Laterality: Asymmetries of Body, Brain and Cognition*, 4, 51-63.
- Helmstaedter, C., Brosch, T., Kurthen, M., & Elger, C. (2004). The impact of sex and language dominance on material-specific memory before and after left temporal lobe surgery. *Brain*, 127, 1518-1525.
- Helmstaedter, C., Grunwald, T., Lehnertz, K., Gleißner, U., & Elger, C. E. (1997). Differential involvement of left temporolateral and temporomesial structures in verbal declarative learning and memory: evidence from temporal lobe epilepsy. *Brain and Cognition*, 35, 110-131.
- Helmstaedter, C., Kurthen, M., Lux, S., Reuber, M., & Elger, C. E. (2003). Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Annals of Neurology*, 54, 425-432.
- Helmstaedter, C., Van Roost, D., Clusmann, H., Urbach, H., Elger, C., & Schramm, J. (2004). Collateral brain damage, a potential source of cognitive impairment after selective surgery for control of mesial temporal lobe epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry*, 75, 323-326.
- Hennion, S., Delbeuck, X., Duhamel, A., Lopes, R., Semah, F., Tyvaert, L., . . . Szurhaj, W. (2014). Characterization and prediction of theory of mind disorders in temporal lobe epilepsy. *Neuropsychology*. doi: 10.1037/neu0000126
- Hermann, B. P., Seidenberg, M., & Bell, B. (2002). The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. *Progress in Brain Research*, 135, 429-438.
- Hermann, B., Seidenberg, M., & Jones, J. (2008). The neurobehavioural comorbidities of epilepsy: can a natural history be developed? *The Lancet Neurology*, 7, 151-160.
- Hermann, B. P., Seidenberg, M., Schoenfeld, J., & Davies, K. (1997). Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Archives of Neurology*, 54, 369-376.

- Heyl, T. (1970). Genealogical study of lipoid proteinosis in South Africa. *The British Journal of Dermatology*, 83, 338-340.
- Hlobil, U., Rathore, C., Alexander, A., Sarma, S., & Radhakrishnan, K. (2008). Impaired facial emotion recognition in patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS): side and age at onset matters. *Epilepsy Research*, 80, 150-157.
- Hurlemann, R., Wagner, M., Hawellek, B., Reich, H., Pieperhoff, P., Amunts, K., . . . Dolan, R. J. (2007). Amygdala control of emotion-induced forgetting and remembering: evidence from Urbach-Wiethe disease. *Neuropsychologia*, 45, 877-884.
- Hyman, B. T., Van Hoesen, G. W., Damasio, A. R., & Barnes, C. L. (1984). Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science*, 225, 1168-1170.
- James, W. (1884). What is an emotion? *Mind*, 9, 188-205.
- Janszky, J., Jokeit, H., Kontopoulou, K., Mertens, M., Ebner, A., Pohlmann-Eden, B., & Woermann, F. G. (2005). Functional MRI predicts memory performance after right mesiotemporal epilepsy surgery. *Epilepsia*, 46, 244-250.
- Janszky, J., Ollech, I., Jokeit, H., Kontopoulou, K., Mertens, M., Pohlmann-Eden, B., . . . Woermann, F. G. (2004). Epileptic activity influences the lateralization of mesiotemporal fMRI activity. *Neurology*, 63, 1813-1817.
- Jokeit, H., & Ebner, A. (1999). Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. *Journal of Neurology, Neurosurgery & Psychiatry*, 67, 44-50.
- Jokeit, H., Ebner, A., Holthausen, H., Markowitsch, H. J., Moch, A., Pannek, H., . . . Tuxhorn, I. (1997). Individual prediction of change in delayed recall of prose passages after left-sided anterior temporal lobectomy. *Neurology*, 49, 481-487.
- Jokeit, H., Okujava, M., & Woermann, F. G. (2001). Memory fMRI lateralizes temporal lobe epilepsy. *Neurology*, 57, 1786-1793.
- Jokeit, H., Seitz, R. J., Markowitsch, H. J., Neumann, N., Witte, O. W., & Ebner, A. (1997). Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain*, 120, 2283-2294.

- Kanner, A. M. (2009). Psychiatric issues in epilepsy: the complex relation of mood, anxiety disorders, and epilepsy. *Epilepsy & Behavior*, 15, 83-87.
- Kanner, A. M., Schachter, S. C., Barry, J. J., Hersdorffer, D. C., Mula, M., Trimble, M., . . . Gilliam, F. (2012). Depression and epilepsy: epidemiologic and neurobiologic perspectives that may explain their high comorbid occurrence. *Epilepsy & Behavior*, 24, 156-168.
- Keller, S. S., & Roberts, N. (2008). Voxel-based morphometry of temporal lobe epilepsy: an introduction and review of the literature. *Epilepsia*, 49, 741-757.
- Kennedy, D. P., & Adolphs, R. (2012). The social brain in psychiatric and neurological disorders. *Trends in Cognitive Sciences*, 16, 559-572.
- Kirsch, H. E. (2006). Social cognition and epilepsy surgery. *Epilepsy & Behavior*, 8, 71-80.
- Klumpers, F., Morgan, B., Terburg, D., Stein, D. J., & van Honk, J. (2014). Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdala damage. *Social Cognitive and Affective Neuroscience*. doi: 10.1093/scan/nsu164
- Klüver, H., & Bucy, P. C. (1937). " Psychic blindness" and other symptoms following bilateral temporal lobectomy in Rhesus monkeys. *American Journal of Physiology*.
- Klüver, H., & Bucy, P. C. (1939). Preliminary analysis of functions of the temporal lobes in monkeys. *Archives of Neurology & Psychiatry*, 42, 979-1000.
- Kobau, R., Dilorio, C. A., Price, P. H., Thurman, D. J., Martin, L. M., Ridings, D. L., & Henry, T. R. (2004). Prevalence of epilepsy and health status of adults with epilepsy in Georgia and Tennessee: behavioral risk factor surveillance system, 2002. *Epilepsy & Behavior*, 5, 358-366.
- Kobau, R., Gilliam, F., & Thurman, D. J. (2006). Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: results from the 2004 Healthstyles Survey. *Epilepsia*, 47, 1915-1921.
- Kobau, R., Zahran, H., Grant, D., Thurman, D. J., Price, P. H., & Zack, M. M. (2007). Prevalence of active epilepsy and health-related quality of life among adults with self-reported epilepsy in California: California Health Interview Survey, 2003. *Epilepsia*, 48, 1904-1913.
- Kupers, R., Fumal, A., de Noordhout, A. M., Gjedde, A., Schoenen, J., & Ptito, M. (2006). Transcranial magnetic stimulation of the visual cortex induces somatotopically organized

- qualia in blind subjects. *Proceedings of the National Academy of Sciences of the United States of America*, 103, 13256-13260.
- Labudda, K., Mertens, M., Steinkroeger, C., Bien, C. G., & Woermann, F. G. (2013). Lesion side matters - an fMRI study on the association between neural correlates of watching dynamic fearful faces and their evaluation in patients with temporal lobe epilepsy. *Epilepsy & Behavior*, 31, 321-328.
- Lange, C. G. (1885). The mechanism of the emotions. In Rand B. (editor), *The Classical Psychologists* (p. 672-685). Boston, MA: Houghton Mifflin.
- Lavenex, P., & Amaral, D. G. (2000). Hippocampal-neocortical interaction: a hierarchy of associativity. *Hippocampus*, 10, 420-430.
- LeDoux, J. E. (1996). *The emotional brain*. New York. Simon and Schuster.
- LeDoux, J. E. (2008). Amygdala. *Scholarpedia*, 3, 2698.
- Leigh, R., Oishi, K., Hsu, J., Lindquist, M., Gottesman, R. F., Jarso, S., . . . Hillis, A. E. (2013). Acute lesions that impair affective empathy. *Brain*, 136, 2539-2549.
- Lespinet, V., Bresson, C., N'Kaoua, B., Rougier, A., & Claverie, B. (2002). Effect of age of onset of temporal lobe epilepsy on the severity and the nature of preoperative memory deficits. *Neuropsychologia*, 40, 1591-1600.
- Li, Y.-H., Chiu, M.-J., Yeh, Z.-T., Liou, H.-H., Cheng, T.-W., & Hua, M.-S. (2013). Theory of Mind in Patients with Temporal Lobe Epilepsy. *Journal of the International Neuropsychological Society*, 19, 594-600.
- Lieb, J. P., Dasheiff, R. M., & Engel, J. (1991). Role of the frontal lobes in the propagation of mesial temporal lobe seizures. *Epilepsia*, 32, 822-837.
- Lieberman, M. D. (2007). Social cognitive neuroscience: a review of core processes. *Annual Review of Psychology*, 58, 259-289.
- Loring, D. W., Marino, S., & Meador, K. J. (2007). Neuropsychological and behavioral effects of antiepilepsy drugs. *Neuropsychology Review*, 17, 413-425.
- Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science*, 280, 921-924.

- Markowitsch, H. J., Calabrese, P., Würker, M., Durwen, H. F., Kessler, J., Babinsky, R., . . . Gehlen, W. (1994). The amygdala's contribution to memory-a study on two patients with Urbach-Wiethe disease. *Neuroreport*, *5*, 1349-1352.
- McClelland, S., 3rd, Garcia, R. E., Peraza, D. M., Shih, T. T., Hirsch, L. J., Hirsch, J., & Goodman, R. R. (2006). Facial emotion recognition after curative nondominant temporal lobectomy in patients with mesial temporal sclerosis. *Epilepsia*, *47*, 1337-1342.
- Meletti, S., Benuzzi, F., Cantalupo, G., Rubboli, G., Tassinari, C. A., & Nichelli, P. (2009). Facial emotion recognition impairment in chronic temporal lobe epilepsy. *Epilepsia*, *50*, 1547-1559.
- Meletti, S., Benuzzi, F., Rubboli, G., Cantalupo, G., Stanzani Maserati, M., Nichelli, P., & Tassinari, C. A. (2003). Impaired facial emotion recognition in early-onset right mesial temporal lobe epilepsy. *Neurology*, *60*, 426-431.
- Meletti, S., Cantalupo, G., Santoro, F., Benuzzi, F., Marliani, A. F., Tassinari, C. A., & Rubboli, G. (2014). Temporal lobe epilepsy and emotion recognition without amygdala: a case study of Urbach-Wiethe disease and review of the literature. *Epileptic Disorders*, *16*, 518-527.
- Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*, *214*, 655-667.
- Mihov, Y., Kendrick, K. M., Becker, B., Zschernack, J., Reich, H., Maier, W., . . . Hurlemann, R. (2013). Mirroring fear in the absence of a functional amygdala. *Biological Psychiatry*, *73*, e9-e11.
- Milner, B. (1972). Disorders of learning and memory after temporal lobe lesions in man. *Clinical Neurosurgery*, *19*, 421-446.
- Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., & Dolan, R. J. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature*, *383*, 812-815.
- Newton, F. H., Rosenberg, R. N., Lampert, P. W., & O'Brien, J. S. (1971). Neurologic involvement in Urbach-Wiethe's disease (lipoid proteinosis): a clinical, ultrastructural, and chemical study. *Neurology*, *21*, 1205-1205.
- Öhman, A., & Mineka, S. (2001). Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological Review*, *108*, 483-522.

- Oyegbile, T., Dow, C., Jones, J., Bell, B., Rutecki, P., Sheth, R., . . . Hermann, B. (2004). The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology*, 62, 1736-1742.
- Paradiso, S., Hermann, B., Blumer, D., Davies, K., & Robinson, R. (2001). Impact of depressed mood on neuropsychological status in temporal lobe epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry*, 70, 180-185.
- Penfield, W., & Milner, B. (1958). Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Archives of Neurology & Psychiatry*, 79, 475-497.
- Perini, G., Tosin, C., Carraro, C., Bernasconi, G., Canevini, M., Canger, R., . . . Testa, G. (1996). Interictal mood and personality disorders in temporal lobe epilepsy and juvenile myoclonic epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry*, 61, 601-605.
- Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience*, 9, 148-158.
- Pessoa, L. (2010). Emotion and cognition and the amygdala: from "what is it?" to "what's to be done?". *Neuropsychologia*, 48, 3416-3429.
- Price, J. L. (1999). Prefrontal cortical networks related to visceral function and mood. *Annals of the New York Academy of Sciences*, 877, 383-396.
- Quiske, A., Helmstaedter, C., Lux, S., & Elger, C. E. (2000). Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. *Epilepsy Research*, 39, 121-125.
- Rankin, K. P., Gorno-Tempini, M. L., Allison, S. C., Stanley, C. M., Glenn, S., Weiner, M. W., & Miller, B. L. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain*, 129, 2945-2956.
- Rausch, R., Kraemer, S., Pietras, C., Le, M., Vickrey, B., & Passaro, E. (2003). Early and late cognitive changes following temporal lobe surgery for epilepsy. *Neurology*, 60, 951-959.
- Ray, R. D., & Zald, D. H. (2012). Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neuroscience & Biobehavioral Reviews*, 36, 479-501.
- Riederer, F., Lanzenberger, R., Kaya, M., Prayer, D., Serles, W., & Baumgartner, C. (2008). Network atrophy in temporal lobe epilepsy: a voxel-based morphometry study. *Neurology*, 71, 419-425.

- Roland, P. E., Eriksson, L., Stone-Elander, S., & Widen, L. (1987). Does mental activity change the oxidative metabolism of the brain? *The Journal of Neuroscience*, 7, 2373-2389.
- Sander, J. W. (2003). The epidemiology of epilepsy revisited. *Current Opinion in Neurology*, 16, 165-170.
- Saxe, R. (2006). Uniquely human social cognition. *Current Opinion in Neurobiology*, 16, 235-239.
- Saxe, R., & Baron-Cohen, S. (2006). Editorial: The neuroscience of theory of mind. *Social Neuroscience*, 1, 1-9.
- Saxe, R., & Powell, L. J. (2006). It's the thought that counts specific brain regions for one component of theory of mind. *Psychological Science*, 17, 692-699.
- Schacher, M., Haemmerle, B., Woermann, F. G., Okujava, M., Huber, D., Grunwald, T., . . . Jokeit, H. (2006). Amygdala fMRI lateralizes temporal lobe epilepsy. *Neurology*, 66, 81-87.
- Schacher, M., Winkler, R., Grunwald, T., Kraemer, G., Kurthen, M., Reed, V., & Jokeit, H. (2006). Mesial temporal lobe epilepsy impairs advanced social cognition. *Epilepsia*, 47, 2141-2146.
- Schacter, D. L., & Tulving, E. (1994). What are the memory systems of 1994? In Schacter D. L. & Tulving E. (editors), *Memory Systems* (p. 1-38). Cambridge, MA: MIT Press.
- Scholz, J., Triantafyllou, C., Whitfield-Gabrieli, S., Brown, E. N., & Saxe, R. (2009). Distinct regions of right temporo-parietal junction are selective for theory of mind and exogenous attention. *PLoS One*, 4, e4869.
- Scott, S. K., Young, A. W., Calder, A. J., Hellawell, D. J., Aggleton, J. P., & Johnsons, M. (1997). Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature*, 385, 254-257.
- Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, 20, 11-21.
- Sedda, A., Rivolta, D., Scarpa, P., Burt, M., Frigerio, E., Zanardi, G., . . . Francione, S. (2013). Ambiguous emotion recognition in temporal lobe epilepsy: the role of expression intensity. *Cognitive, Affective, & Behavioral Neuroscience*, 13, 452-463.
- Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., . . . Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience*, 27, 2349-2356.

- Selwa, L. M., Berent, S., Giordani, B., Henry, T. R., Buchtel, H. A., & Ross, D. A. (1994). Serial cognitive testing in temporal lobe epilepsy: longitudinal changes with medical and surgical therapies. *Epilepsia*, *35*, 743-749.
- Shamay-Tsoory, S., Tomer, R., Berger, B., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *Journal of Cognitive Neuroscience*, *15*, 324-337.
- Shaw, P., Lawrence, E., Bramham, J., Brierley, B., Radbourne, C., & David, A. (2007). A prospective study of the effects of anterior temporal lobectomy on emotion recognition and theory of mind. *Neuropsychologia*, *45*, 2783-2790.
- Shaw, P., Lawrence, E., Radbourne, C., Bramham, J., Polkey, C., & David, A. (2004). The impact of early and late damage to the human amygdala on 'theory of mind' reasoning. *Brain*, *127*, 1535-1548.
- Sherman, E., Griffiths, S. Y., Akdag, S., Connolly, M. B., Slick, D. J., & Wiebe, S. (2008). Sociodemographic correlates of health-related quality of life in pediatric epilepsy. *Epilepsy & Behavior*, *12*, 96-101.
- Siebert, M., Markowitsch, H. J., & Bartel, P. (2003). Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. *Brain*, *126*, 2627-2637.
- Singer, T., Critchley, H. D., & Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences*, *13*, 334-340.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, *303*, 1157-1162.
- Sporns, O., Honey, C. J., & Kötter, R. (2007). Identification and classification of hubs in brain networks. *PloS One*, *2*, e1049.
- Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review*, *99*, 195-231.
- Squire, L. R., Schmolck, H., & Stark, S. M. (2001). Impaired auditory recognition memory in amnesic patients with medial temporal lobe lesions. *Learning & Memory*, *8*, 252-256.
- Squire, L. R., Zola-Morgan, S., & Chen, K. S. (1988). Human amnesia and animal models of amnesia: performance of amnesic patients on tests designed for the monkey. *Behavioral Neuroscience*, *102*, 210-221.

- Staut, C. C., & Naidich, T. P. (1998). Urbach-Wiethe disease (Lipoid proteinosis). *Pediatric Neurosurgery*, 28, 212-214.
- Strine, T. W., Kobau, R., Chapman, D. P., Thurman, D. J., Price, P., & Balluz, L. S. (2005). Psychological distress, comorbidities, and health behaviors among US adults with seizures: results from the 2002 National Health Interview Survey. *Epilepsia*, 46, 1133-1139.
- Stroup, E., Langfitt, J., Berg, M., McDermott, M., Pilcher, W., & Como, P. (2003). Predicting verbal memory decline following anterior temporal lobectomy (ATL). *Neurology*, 60, 1266-1273.
- Struiksma, M. E., Noordzij, M. L., & Postma, A. (2009). What is the link between language and spatial images? Behavioral and neural findings in blind and sighted individuals. *Acta Psychologica*, 132, 145-156.
- Szemere, E., & Jokeit, H. (2015). Quality of life is social—towards an improvement of social abilities in patients with epilepsy. *Seizure*, 26, 12-21.
- Takaya, S., Hanakawa, T., Hashikawa, K., Ikeda, A., Sawamoto, N., Nagamine, T., . . . Fukuyama, H. (2006). Prefrontal hypofunction in patients with intractable mesial temporal lobe epilepsy. *Neurology*, 67, 1674-1676.
- Tanaka, A., Akamatsu, N., Yamano, M., Nakagawa, M., Kawamura, M., & Tsuji, S. (2013). A more realistic approach, using dynamic stimuli, to test facial emotion recognition impairment in temporal lobe epilepsy. *Epilepsy & Behavior*, 28, 12-16.
- Téllez-Zenteno, J. F., & Hernández-Ronquillo, L. (2011). A review of the epidemiology of temporal lobe epilepsy. *Epilepsy Research and Treatment*, 2012, 1-5.
- Terburg, D., Morgan, B. E., Montoya, E. R., Hooge, I. T., Thornton, H. B., Hariri, A. R., . . . van Honk, J. (2012). Hypervigilance for fear after basolateral amygdala damage in humans. *Translational Psychiatry*, 2, e115.
- Thornton, H. B., Nel, D., Thornton, D., van Honk, J., Baker, G. A., & Stein, D. J. (2008). The neuropsychiatry and neuropsychology of lipoid proteinosis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 20, 86-92.
- Tomasi, D., & Volkow, N. D. (2011). Association between functional connectivity hubs and brain networks. *Cerebral Cortex*, 21, 2003-2013.

- Tranel, D., Gullickson, G., Koch, M., & Adolphs, R. (2006). Altered experience of emotion following bilateral amygdala damage. *Cognitive Neuropsychiatry*, *11*, 219-232.
- Urbach, E., & Wiethe, C. (1929). Lipoidosis cutis et mucosae. *Virchows Archiv*, *273*, 285-319.
- Van Houghenouck-Tulleken, W., Chan, I., Hamada, T., Thornton, H., Jenkins, T., McLean, W. H., . . . Ramsay, M. (2004). Clinical and molecular characterization of lipid proteinosis in Namaqualand, South Africa. *The British Journal of Dermatology*, *151*, 413-423.
- van Stegeren, A. H., Everaerd, W., & Gooren, L. J. (2002). The effect of beta-adrenergic blockade after encoding on memory of an emotional event. *Psychopharmacology*, *163*, 202-212.
- Waxman, S. G., & Geschwind, N. (1975). The interictal behavior syndrome of temporal lobe epilepsy. *Archives of General Psychiatry*, *32*, 1580-1586.
- Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *The Journal of Neuroscience*, *18*, 411-418.
- Wicker, B., Keysers, C., Plailly, J., Royet, J.-P., Gallese, V., & Rizzolatti, G. (2003). Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. *Neuron*, *40*, 655-664.
- Winocur, G., McDonald, R. M., & Moscovitch, M. (2001). Anterograde and retrograde amnesia in rats with large hippocampal lesions. *Hippocampus*, *11*, 18-26.
- Young, M. P., Scanneil, J. W., Burns, G. A., & Blakemore, C. (1994). Analysis of connectivity: neural systems in the cerebral cortex. *Reviews in the Neurosciences*, *5*, 227-250.
- Zola-Morgan, S., Squire, L. R., & Ramus, S. J. (1994). Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. *Hippocampus*, *4*, 483-495.

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Supervision of master thesis

2012-2014 Katharina Ledergerber (2014). „Act naturally“: An explorative fMRI study on the art of acting.

Grants

Aug-Sep 2014 **Travel Grant** by the Neuroscience Center Zurich, ETH/University of Zurich, for the multicenter project “A pilot study on the etiopathogenesis of impaired social cognition in patients with Urbach-Wiethe disease”.

Aug-Sep 2014 **Travel Grant** by the PhD Program Psychology, University of Zurich, for the multicenter project “A pilot study on the etiopathogenesis of impaired social cognition in patients with Urbach-Wiethe disease”.

Sep 2013 **International Short Visit Grant** by the Swiss National Foundation
for the multicenter project “A pilot study on the etiopathogenesis of impaired social cognition in patients with Urbach-Wiethe disease”.
PI: Prof. Hennric Jokeit, PhD.

Award

Mai 2013 **Poster award: Toller G**, Broicher SD, Grunwald T, Huber D, Krämer G, Kurthen M, Jokeit H. Unilateral mesial temporal epilepsy impairs remote brain activation and social cognition. 8. *Gemeinsame Jahrestagung der Deutschen und Österreichischen Gesellschaften für Epileptologie und der Schweizerischen Liga gegen Epilepsie, Interlaken, Switzerland, 8-11 Mai 2013.*

Publications (peer-reviewed)

Toller G, Adhimoolam B, Grunwald T, Huppertz HJ, König K, Jokeit H. Nonvisual spatial navigation lateralizes mesial temporal lobe epilepsy in a patient with congenital blindness. *Neurocase*, 2014.

Toller G, Adhimoolam B, Grunwald T, Huppertz HJ, Kurthen M, Rankin K, Jokeit H. Right mesial temporal lobe epilepsy impairs empathy-related brain responses to dynamic fearful faces. *Journal of Neurology*, 2015.

Toller G, Adhimoolam B, Rankin KP, Huppertz HJ, Kurthen M, Jokeit H. Right fronto-limbic atrophy is associated with reduced empathy in refractory unilateral mesial temporal lobe epilepsy. *Neuropsychologia*, 2015.

Toller G, Ives-Deliperi V, Butler J, Rauch L, Evans R, Jokeit H. Amygdala dysfunction with preserved psychophysiological and subjective arousal in two patients with Urbach-Wiethe disease. Submitted.

Talks

Neuroscience Meeting, Mediclinic Constantiaberg, Cape Town, South Africa

Title: Mesial temporal lobe epilepsy impairs social cognition.

Date: 5 September 2014

Brain Fair 2014, Program for schools, Neuroscience Center Zurich, Switzerland

Title: Blick ins Gehirn von Epilepsie-Patienten.

Dates: 5 and 11 March 2014

16èmes Journées Françaises de l'Epilepsie, Lille, France

Title: Mesial temporal lobe epilepsy impairs social cognition and remote brain activation.

Date: 5 November 2013

30th International Epilepsy Congress, Montreal, Canada

Title: Unilateral mesial temporal lobe epilepsy impairs remote brain activation and social cognition.

Date: 25 June 2013

PhD retreat, International PhD Program in Neuroscience, Valens, Switzerland

Title: Unilateral mesial temporal lobe epilepsy impairs remote brain activation and social cognition.

Date: 26 April 2013

Posters

Toller G, Adhimoolam B, Grunwald T, Huppertz HJ, König K, Jokeit H. Nonvisual spatial navigation lateralizes mesial temporal lobe epilepsy in a patient with congenital blindness. *ZNZ (Neuroscience Center Zurich) Symposium, Zurich, Switzerland*, 11 September 2014.

Ledergerber K, **Toller G**, Kiefer J, Jokeit H. "Your inside is out, and your outside is in?"

An fMRI case study on the art of acting. *Neuro Epilepsy Day, Montreal Neurological Institute and Hospital, Montreal, Canada, 6 March 2014.*

Toller G, Broicher SD, Grunwald T, Huber D, Huppertz HJ, Krämer G, Kurthen M, Jokeit H. Unilateral mesial temporal epilepsy impairs remote brain activation and social cognition. *ZNZ (Neuroscience Center Zurich) Symposium, Zurich, Switzerland, 13 September 2013.*

Toller G, Broicher SD, Grunwald T, Huber D, Krämer G, Kurthen M, Jokeit H. Unilateral mesial temporal epilepsy impairs remote brain activation and social cognition. *8. Gemeinsame Jahrestagung der Deutschen und Österreichischen Gesellschaften für Epileptologie und der Schweizerischen Liga gegen Epilepsie, Interlaken, Switzerland, 8-11 Mai 2013.*

Toller G, Broicher SD, Huber D, Jokeit H. A qualitative analysis of emotional reactivity to animated fearful faces measured by fMRI in patients with mesial temporal lobe epilepsy and healthy controls. *ZNZ (Neuroscience Center Zurich) Symposium, Zurich, Switzerland, 30 August 2012.*

Toller G, Broicher SD, Huber D, Jokeit J. A qualitative analysis of emotional reactivity to animated fearful faces measured by fMRI in patients with mesial temporal lobe epilepsy and healthy controls. *Interdisciplinary Conference on Social Cognition, Engagement and the Second-Person-Perspective, University of Cologne, Germany, 27 Mai 2012.*

Toller G, Broicher SD, Huber D, Jokeit J. A qualitative and normative analysis of fMRI reactivity to animated fearful faces in healthy controls. *2nd International Congress on Epilepsy, Brain and Mind, Prague, Czech Republic, 30 March 2012.*

Toller G, Gutbrod K, Müri R, Meier B. Increased prospective memory performance in patients with dense amnesia after repetitive feedback and after a delay of 24 hours. *Clinical Neuroscience Bern Meeting, Bern, Switzerland, 1 December 2009.*